WEST Search History

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updated search 11/05 RP

DATE: Wednesday, November 02, 2005

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L1	lumen same (toxin or neurotoxin or neuro-toxin or botox or botulinum or tetanus or tetrodotoxin or bungotoxin or terodotoxin or conotoxin or cono-toxin or bungo or terodo or tetrodo or btn or btx or bta or rbtn)	366
☐	L2	lumen near50 (toxin or neurotoxin or neuro-toxin or botox or botulinum or tetanus or tetrodotoxin or bungotoxin or terodotoxin or conotoxin or cono-toxin or bungo or terodo or tetrodo or btn or btx or bta or rbtn)	162
☐	L3	lumen.clm. near50 (toxin or neurotoxin or neuro-toxin or botox or botulinum or tetanus or tetrodotoxin or bungotoxin or terodotoxin or conotoxin or cono-toxin or bungo or terodo or tetrodo or btn or btx or bta or rbtn).clm.	17
☐	L4	lumen near10 bladder	1260
☐	L5	L4 and l1	5
☐	L6	(urologic or urinary or urology or bladder or detrusor or hyperreflexia or neurogenic or incontinence or irritable or spastic or unstable or hypertonic or uninhibited or dyssynergic or systolic)same bladder same lumen	2376
☐	L7	L6 and l1	10
☐	L8	L7 not l3	10
☐	L9	neurotoxin near5 bladder	3
☐	L10	neurotoxin near5 lumen	5
☐	L11	L10 not l5	3
☐	L12	L11 not l3	3

END OF SEARCH HISTORY

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DATE: Wednesday, November 02, 2005

Hide?	Set Name	Query	Hit Count
		DB=USPT; PLUR=YES; OP=OR	
☐	L1	bladder near3 lumen	318
☐	L2	L1 and (toxin or neurotoxin or neurotoxin or $toxin)	18

END OF SEARCH HISTORY

. 20040260272. 22 Oct 03. 23 Dec 04. Method and system for intravesicular delivery of therapeutic agents. Friedman, Craig D., et al. 604/890.1; A61K009/22.

☐ 2. 20040067235. 25 Jul 03. 08 Apr 04. Methods for the use of neurotoxin in the treatment of urologic disorders. Doshi, Rajiv. 424/184.1; A61K039/00 A61K039/38.

☐ 3. 20030161809. 02 Oct 01. 28 Aug 03. Compositions and methods for the transport of biologically active agents across cellular barriers. Houston, L. L., et al. 424/85.2; 424/178.1 435/6 514/44 530/351 530/391.1 530/395 A61K039/395 C12Q001/68 A61K038/20 A61K048/00 C07K014/52 C07K016/46.

☐ 4. 5824493. 23 Feb 96; 20 Oct 98. Diagnostic test for interstitial cystitis. Elgavish; Ada. 435/29; 424/558 435/30 435/34 435/374 435/377 435/378 435/383 435/391 435/404 435/7.1 435/7.2 435/7.21 436/63 436/74. C12Q001/02 C12Q001/04 G01N033/53 G01N033/20.

☐ 5. WO2004010934A2. 25 Jul 03. 05 Feb 04. METHODS FOR THE USE OF NEUROTOXIN IN THE TREATMENT OF UROLOGIC DISORDERS. DOSHI, RAJIV. A61K00/;.

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Search Results - Record(s) 1 through 10 of 10 returned.

☐ 1. 20050090732. 28 Oct 03. 28 Apr 05. Therapy via targeted delivery of nanoscale particles. Ivkov, Robert, et al. 600/411; 324/318 A61B005/055.

☐ 2. 20050084514. 08 Jul 04. 21 Apr 05. Combination drug therapy for reducing scar tissue formation. Shebuski, Ronald J., et al. 424/426; 514/291 514/571 604/500 A61K031/4745 A61K031/192 A61F002/00.

☐ 3. 20040260272. 22 Oct 03. 23 Dec 04. Method and system for intravesicular delivery of therapeutic agents. Friedman, Craig D., et al. 604/890.1; A61K009/22.

☐ 4. 20040156852. 06 Feb 03. 12 Aug 04. Therapy via targeted delivery of nanoscale particles. Daum, Wolfgang, et al. 424/155.1; 424/178.1 604/20 A61K039/395 A61N001/30.

☐ 5. 20040067235. 25 Jul 03. 08 Apr 04. Methods for the use of neurotoxin in the treatment of urologic disorders. Doshi, Rajiv. 424/184.1; A61K039/00 A61K039/38.

☐ 6. 20030161809. 02 Oct 01. 28 Aug 03. Compositions and methods for the transport of biologically active agents across cellular barriers. Houston, L. L., et al. 424/85.2; 424/178.1 435/6 514/44 530/351 530/391.1 530/395 A61K039/395 C12Q001/68 A61K038/20 A61K048/00 C07K014/52 C07K016/46.

☐ 7. 5824493. 23 Feb 96; 20 Oct 98. Diagnostic test for interstitial cystitis. Elgavish; Ada. 435/29; 424/558 435/30 435/34 435/374 435/377 435/378 435/383 435/391 435/404 435/7.1 435/7.2 435/7.21 436/63 436/74. C12Q001/02 C12Q001/04 G01N033/53 G01N033/20.

☐ 8. 5459068. 17 Nov 93; 17 Oct 95. Microassay system for assessing transmigration of PMN across epithelia in a serosal-to-mucosal direction. Madara; James L.. 435/287.1; 435/287.2 435/287.9 435/288.1. C12M003/06 C12M001/34 C12M001/42.

☐ 9. WO2004010934A2. 25 Jul 03. 05 Feb 04. METHODS FOR THE USE OF NEUROTOXIN IN THE TREATMENT OF UROLOGIC DISORDERS. DOSHI, RAJIV. A61K00/;.

☐ 10. US 5840713A. Admin. of oligosaccharide, partic. cyclic anionic oligosaccharide - for reducing leakage of protein substances through tissue membrane and treating or preventing e.g. nephropathies and glomerulopathies. WEISZ, P B. A61K031/00 A61K031/70 A61K031/715 A61K031/725 C08B031/16 C08B037/16.

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Term	Documents
(7 NOT 3).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	10
(L7 NOT L3).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	10

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US 20040226556A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2004/0226556 A1

Deem et al. (43) Pub. Date: Nov. 18, 2004

(54) APPARATUS FOR TREATING ASTHMA USING NEUROTOXIN

(76) Inventors: Mark E. Deem, Mountain View, CA (US); Hanson S. Gifford, Woodside, CA (US)

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(21) Appl. No.: 10/437,882

(22) Filed: May 13, 2003

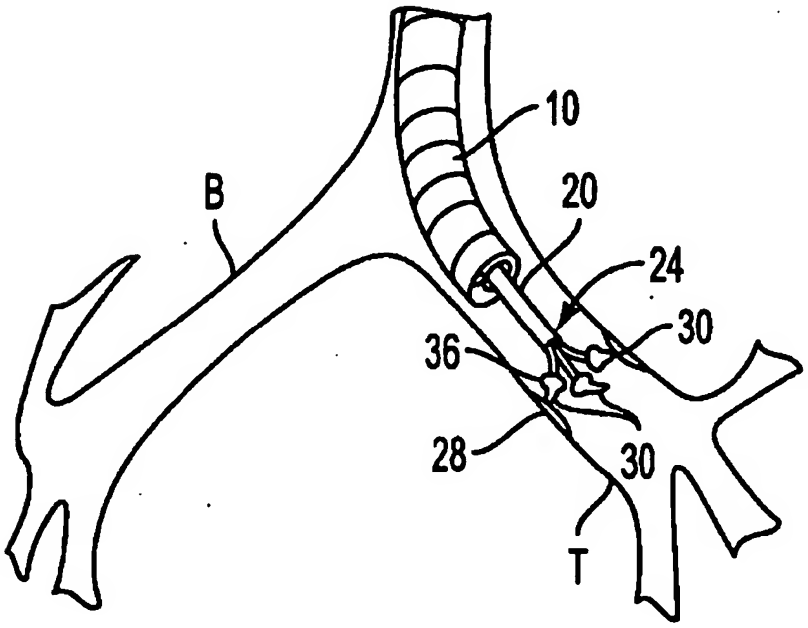
Publication Classification

(51) Int. Cl.[7] A61M 15/00; A61M 16/00

(52) U.S. Cl. 128/200.24

(57) ABSTRACT

Apparatus providing intrabronchial delivery of neurotoxin to control the effects of asthma comprises a shaft having proximal and distal ends and a neurotoxin applicator assembly disposed on the distal end, wherein the neurotoxin applicator assembly comprises a deployable needle assembly, a rotating needle assembly, a needle-less injection assembly or a nebulizer assembly.



DOCUMENT-IDENTIFIER: US 20040226556 A1
TITLE: Apparatus for treating asthma using neurotoxin

Summary of Invention Paragraph:
[0019] In a first illustrative embodiment, the neurotoxin applicator assembly comprises a needle assembly including at least one needle having a lumen in fluid communication with a source of liquid neurotoxin. The needles are preformed to contract radially when disposed within a lumen, such as a lumen of the bronchoscope, but may be extended to penetrate and inject small doses of neurotoxin into the bronchial wall of a patient.

Summary of Invention Paragraph:
[0020] In an alternative embodiment, the neurotoxin applicator assembly comprises a rotating needle assembly including plural needles disposed along the circumference of a wheel. Again, the needles include lumens in fluid communication with a source of liquid neurotoxin. In operation, the wheel is adapted to be rolled across a target treatment area about a central hub. Optionally, the rotating needle assembly may include a fender to protect a portion of the bronchial wall substantially opposite the target treatment area.

Detail Description Paragraph:
[0034] In accordance with the principles of the present invention, neurotoxin applicator assembly 20, of which various illustrative embodiments are described hereinbelow, enables the physician to selectively administer controlled doses of neurotoxin to or within selected treatment sites in the patient's lung. More specifically, neurotoxin applicator assembly 20 may be selectively advanced through lumen 14 of bronchoscope 10 to deliver a neurotoxin, such as botulinum toxin, serotype A, to a target treatment area.

Detail Description Paragraph:
[0035] Neurotoxin applicator assembly 20 includes shaft 21 coupled to at its proximal end to handle 22, distal end 23 having neurotoxin applicator 24, and lumen 25. Lumen 25 provides fluid communication between proximal end and handle 22 and applicator 24. Syringe 26 having plunger 27 is coupled to a port on proximal end 22. Syringe 26 is filled with neurotoxin in liquid form, and applies the neurotoxin to applicator 24 via lumen 25 when plunger 27 is actuated.

DOCUMENT-IDENTIFIER: US 20030161809 A1
TITLE: Compositions and methods for the transport of biologically active agents across cellular barriers

Summary of Invention Paragraph:
[0022] Adjacent epithelial cells are connected by tight junctions. Disruption of tight junctions allows agents within the lumen, which often has an opening to the external environment of an animal, to penetrate into the body. Although such agents might include therapeutic agents, entry into the body via a disrupted tight junction is not specific; undesirable agents (e.g., bacteria, viruses, toxins and the like) will also be taken into the body. Due to this lack of specificity, as well as other factors, disruption of tight junctions for drug delivery purposes is generally not feasible and would, in any event, have many potential undesirable side effects.

Summary of Invention Paragraph:
[0104] Epithelial cells, representing a cellular barrier. line the interior of said lumen. Lumen of particular interest include, by way of non-limiting example, gastrointestinal lumen, the pulmonary lumen, the nasal lumen, a nasopharyngeal lumen, a pharyngeal lumen, a buccal lumen, a sublingual lumen, a vaginal lumen, a urogenital lumen, an ocular lumen, a tympanic lumen, an ocular surface, uterine, urethral, bladder, mammary, salivary, lacrimal, respiratory sinus, biliary, sweat gland.

CLAIMS:

34. The complex or compound of claim 31 or 32, wherein said lumen is selected from the group consisting of an gastrointestinal lumen, the pulmonary lumen, the nasal lumen, a nasopharyngeal lumen, a pharyngeal lumen, a buccal lumen, a sublingual lumen, a vaginal lumen, a urogenital lumen, an ocular lumen, a tympanic lumen, an ocular surface, uterine, urethral, bladder, mammary, salivary, lacrimal, respiratory sinus, biliary, sweat gland.

L3: Entry 13 of 17 File: USPT Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180356 B1
TITLE: Membrane pore inhibiting agents for treating infection

CLAIMS:

7. A method according to claim 1, wherein the method comprises, preparing an aqueous solution, in which bacterial toxin can form pores in membranes, of phospholipid vesicles which contain fluorescent reporter in the lumen; introducing target agent and pore forming toxin to the solution and incubating; measuring the fluorescence of the solution; introducing quencher to the solution; and again measuring the fluorescence of the solution to determine the quenching of the fluorescent reporter group that has passed through the membrane, and thus assaying pore formation in the membrane.

10. A method according to claim 1, wherein the method comprises, preparing an aqueous solution, in which bacterial toxin can form pores in membranes, of phospholipid vesicicles which contain quencher in the lumen; introducing target agent and pore forming toxin to the solution and incubating; introducing fluorescent reporter to the solution; and measuring fluorescence of the solution and comparing that fluorescence to fluorescence of a similar sample lacking toxin to determine the quenching of the fluorescent reporter that has passed through the membrane, and thus assaying pore formation in the membrane.

19. A method according to claim 13, wherein the method comprises preparing an aqueous solution, in which Diphtheria toxin can form pores in membranes, of phospholipid vesicles which contain fluorescent reporter in the lumen; introducing the target agent and the Diphtheria toxin protein to the solution and incubating; measuring the fluorescence of the solution; introducing quencher to the solution; and again measuring the fluorescence of the solution to determine the quenching of the fluorescent reporter group that has passed through the membrane, and thus assaying pore formation in the membrane.

22. A method according to claim 13, wherein the method comprises, preparing an aqueous solution, in which Diphtheria toxin can form pores in membranes, of phospholipid vesicles which contain quencher in the lumen; introducing the target agent and the Diphtheria toxin protein to the solution and incubating; introducing fluorescent reporter to the solution; and measuring fluorescence of the solution and comparing that fluorescence to fluorescence of a similar sample lacking Diphtheria toxin to determine the quenching of the fluorescent reporter that has passed through the membrane, and thus assaying pore formation in the membrane.

L3: Entry 15 of 17 File: USPT Apr 21, 1998

DOCUMENT-IDENTIFIER: US 5741807 A
TITLE: Histidine compositions and methods for treating or preventing infectious and non-infectious diarrheas

CLAIMS:

23. A method of preventing or reducing at least one of intestinal tract fluid secretions, fluid loss, or electrolyte loss in a mammal having diarrhea as a result of at least one of Salmonella typhimurium or Cholera toxin, by administering to at least one of peritoneum and intestinal lumen of said mammal a therapeutically effective amount of at least one of D-histidine, L-histidine, a racemic mixture thereof, a nonracemic mixture thereof, or pharmaceutically acceptable salts thereof.

DERWENT-ACC-NO: 1997-212558
DERWENT-WEEK: 200025

TITLE: Admin. of oligosaccharide, partic. cyclic anionic oligosaccharide - for reducing leakage of protein substances through tissue membrane and treating or preventing e.g. nephropathies and glomerulopathies

INVENTOR: WEISZ, P B

PATENT-ASSIGNEE: WEISZ P B (WEISI)

PRIORITY-DATA: 1995US-0530777 (September 19, 1995), 1995US-0416107 (April 3, 1995)

Search Selected | Search ALL | Clear

PATENT-FAMILY:

	PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
☐	WO 9710828 A1	March 27, 1997	E	031	A61K031/70
☐	HU 9903538 A2	March 28, 2000		000	A61K031/70
☐	EP 861082 A1	September 2, 1998	E	000	A61K031/70
☐	US 5840713 A	November 24, 1998		000	A61K031/715
☐	JP 11512479 W	October 26, 1999		020	C08B037/16

DESIGNATED-STATES: HU JP AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

CITED-DOCUMENTS:3.Jnl.Ref; EP 431735 ; US 5019562 ; US 5093106

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 9710828A1	September 17, 1996	1996WO-US14511	
HU 9903538A2	September 17, 1996	1996WO-US14511	
HU 9903538A2	September 17, 1996	1999HU-0003538	
HU 9903538A2		WO 9710828	Based on
EP 861082A1	September 17, 1996	1996EP-0931514	
EP 861082A1	September 17, 1996	1996WO-US14511	
EP 861082A1		WO 9710828	Based on
US 5840713A	April 3, 1995	1995US-0416107	CIP of
US 5840713A	September 19, 1995	1995US-0530777	
US 5840713A		US 5760015	CIP of
JP 11512479W	September 17, 1996	1996WO-US14511	
JP 11512479W	September 17, 1996	1997JP-0512761	
JP 11512479W		WO 9710828	Based on

INT-CL (IPC): A61 K 31/00; A61 K 31/70; A61 K 31/715; A61 K 31/725; C08 B 31/16; C08 B 37/16

RELATED-ACC-NO: 1989-233735;1993-066455 ;1993-182233 ;1993-377468 ;1995-292509 ;1996-251040 ;1996-464758 ;1997-212585

ABSTRACTED-PUB-NO: US 5840713A
BASIC-ABSTRACT:

Method for reducing pathologically excessive permeability of tissue membranes to leakage of protein substances comprises admin. of an oligosaccharide (I) comprising at most 10 sugar units, substd. with at least 1.4 anionic gps. per sugar mol. Also claimed are: (1) admin. of a cyclic anionic polysaccharide agent by rectal delivery of a soln. comprising the polysaccharide in a physiologically acceptable solvent, and (2) admin. of (I) by inhalation of a nebulised soln. of (I) in a physiologically acceptable solvent, or by retrograde irrigation of the bladder with (I) in a physiologically acceptable solvent.

USE - (I) can be used: (a) to reduce excretion of albumin in urine resulting from an insufficiently functioning glomerular membrane of the kidney; (b) to reduce leakage of protein components into the lumen of the intestine resulting from an insufficiently functioning membrane of the intestine (e.g. Crohn's disease); (c) to reduce leakage of protein components into the bladder resulting from an insufficiently functioning epithelial barrier due to an inflammatory condition (e.g. interstitial cystitis), or (d) to reduce leakage into the lung as a result of insufficient lung performance due to asthma (all claimed).(I) can be used to treat or prevent nephropathies and glomerulopathies, e.g. caused or aggravated by toxins, bacterial agents, chronic serum disease, diabetes mellitus and hypertension; inflammatory pathologies of the bowel; and by admin. to the olfactory system, to arrest leakage of foreign matter (e.g. Al contg. entities) to the brain preventing development or progression of brain lesions (e.g. in Alzheimer's disease). Admin. is carried out by conventional routes, e.g. intra venous, subcutaneous and intraperitoneal (claimed). The daily dosage is 0.1-10 (esp. 0.1-1)mg/kg parenterally. For the treatment of the pulmonary system, daily dosage is <1 (esp. 0.01-1)mg/kg. Oral admin. is used esp. for urinary or gastrointestinal conditions. Disease of the bladder or intestines is treated by direct irrigation by infusion of fluids contg. (I) (0.1-10mg/ml).

ADVANTAGE - (I) do not possess antithrombin activity, and can therefore be used at effective dosage levels at which heparin could not be used due to its anticoagulant activity (leading to serious side effects). Also, (I) are easily and economically synthesised from available cyclo-oligosaccharides, unlike heparin.

ABSTRACTED-PUB-NO: WO 9710828A
EQUIVALENT-ABSTRACTS:

Method for reducing pathologically excessive permeability of tissue membranes to leakage of protein substances comprises admin. of an oligosaccharide (I) comprising at most 10 sugar units, substd. with at least 1.4 anionic gps. per sugar mol. Also claimed are: (1) admin. of a cyclic anionic polysaccharide agent by rectal delivery of a soln. comprising the polysaccharide in a physiologically acceptable solvent, and (2) admin. of (I) by inhalation of a nebulised soln. of (I) in a physiologically acceptable solvent, or by retrograde irrigation of the bladder with (I) in a physiologically acceptable solvent.

USE - (I) can be used: (a) to reduce excretion of albumin in urine resulting from an insufficiently functioning glomerular membrane of the kidney; (b) to reduce leakage of protein components into the lumen of the intestine resulting from an insufficiently functioning membrane of the intestine (e.g. Crohn's disease); (c) to reduce leakage of protein components into the bladder resulting from an

insufficiently functioning epithelial barrier due to an inflammatory condition (e.g. interstitial cystitis), or (d) to reduce leakage into the lung as a result of insufficient lung performance due to asthma (all claimed).(I) can be used to treat or prevent nephropathies and glomerulopathies, e.g. caused or aggravated by toxins, bacterial agents, chronic serum disease, diabetes mellitus and hypertension; inflammatory pathologies of the bowel; and by admin. to the olfactory system, to arrest leakage of foreign matter (e.g. Al contg. entities) to the brain preventing development or progression of brain lesions (e.g. in Alzheimer's disease). Admin. is carried out by conventional routes, e.g. intra venous, subcutaneous and intraperitoneal (claimed). The daily dosage is 0.1-10 (esp. 0.1-1)mg/kg parenterally. For the treatment of the pulmonary system, daily dosage is <1 (esp. 0.01-1)mg/kg. Oral admin. is used esp. for urinary or gastrointestinal conditions. Disease of the bladder or intestines is treated by direct irrigation by infusion of fluids contg. (I) (0.1-10mg/ml).

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CHOSEN-DRAWING: Dwg.0/0

DERWENT-CLASS: B04
CPI-CODES: B04-C02X; B14-E10; B14-K01A; B14-N07B; B14-N10;

US 20040013687A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2004/0013687 A1

Simpson et al. (43) Pub. Date: Jan. 22, 2004

(54) COMPOSITIONS AND METHODS FOR TRANSEPITHELIAL MOLECULAR TRANSPORT

(75) Inventors: Lance Simpson, Moorestown, NJ (US); Andrew Maksymowych, Gulph Mills, PA (US); Jung-Beak Park, Philadelphia, PA (US)

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(73) Assignee: Thomas Jefferson University

(21) Appl. No.: 10/452,024

(22) Filed: Jun. 2, 2003

Related U.S. Application Data

(60) Provisional application No. 60/384,949, filed on May 31, 2002.

Publication Classification

(51) Int. Cl.[7] A61K 39/02

(52) U.S. Cl. 424/190.1

(57) ABSTRACT

The invention relates to fragments of *Clostridium botulinum* HC that can be linked with an entity (e.g., an antigen, a particle, or a radionuclide) and used to deliver the entity across a non-keratinized epithelial membrane of an animal. The fragments are useful, for example, for making vaccines, antidotes, and anti-toxins and in situations in which rapid uptake of an agent by an animal is desired.

DOCUMENT-IDENTIFIER: US 20040013687 A1
TITLE: Compositions and methods for transepithelial molecular transport

Detail Description Paragraph:
[0369] Animals were anesthetized by administration of Isoflurane (ISO-THESIA.TM., Abbott Laboratories North, Chicago, Ill., U.S.A.) and oxygen, and this same inhalation anesthetic was administered throughout surgery. An abdominal laparotomy (about 1.5 to 2.5 centimeters, depending on the size of the mouse) was performed, and either the stomach or the small intestine immediately proximal to the stomach was partially externalized. If required by protocol, a ligature was placed immediately above (proximal to the stomach) the pyloric sphincter using 3-0 PROLENE.TM. (polypropylene suture, Ethicon, Inc., Somerville, N.J., U.S.A.). Care was taken so that this ligature was sufficient to prevent flow of stomach juices into the intestine (or reverse flow of intestinal contents into the stomach), but not sufficient to cause mechanical damage to the tissues involved. Neurotoxin was administered through a 1 milliliter tuberculin syringe with a 0.5 inch, 27 gauge needle. Injection volumes were kept constant at 100 microliters per animal regardless of site of administration (stomach or intestine). For all injections, the vehicle consisted of sterile Dulbecco's PBS (pH 7.4) with 1 milligram BSA per milliliter. Neurotoxin was administered into the lumen of the stomach by injection through the stomach wall at the greater curvature, with care to avoid the gastro-epiploic vessels. Neurotoxin was administered into the lumen of the small intestine by oblique insertion of the needle parallel to the segment and always in a direction away from the stomach. The time of injection was recorded.

L2: Entry 12 of 18 File: USPT Jul 14, 1998

DOCUMENT-IDENTIFIER: US 5779661 A
TITLE: Method of treating dysfunctional bladder syndromes by electromotive drug administration

Brief Summary Text (27):
Electroporation is a term newly coined by Prausnitz et al. (Transdermal drug delivery by electroporation. Abstract Proceed. Intern. Symp. Control. Rel. Bioact. Mat. 1992;19.) and is used to describe a phenomenon known for many years: it was described by Jung et al. in 1983 (Conformational requirements for the potential dependent pore formation of the peptide antibiotics alamethicin, suzukacillin and trichotoxin. In: Spach G ed. Physical Chemistry of Transmembrane Ion Motion. New York: Elsevier; 1983). Application of an electric field causes an increase in the permeability of biological membranes and thus there is increased transport of drugs down concentration gradients because the value of the diffusion coefficient (D) has been increased.

Brief Summary Text (30):
With an incidence approaching 100%, pathogenic microorganisms gain access to the bladder, either down the lumen of the catheter or, more importantly, between the external walls of the catheter and the distorted (and therefore "defenceless") surrounding tissues: the urethra or the incision in the abdominal wall. Once within the bladder, the micro-organisms multiply within "privileged" sites provided by the intravesical portion of the catheter and rapidly become resistant to most, if not all, antimicrobial agents. Moreover, the catheter constantly irritates and inflames the bladder wall so that, over time, the combination of chronic infection and mechanical irritation causes scarring and contraction of the bladder, damage to the ureters and consequent upper urinary tract obstruction and eventually kidney failure. Many patients with permanent bladder catheter are treated with artificial kidneys because of kidney failure and countless numbers have died of overwhelming infections caused by the resistant microorganisms residing in a catheterized bladder.

L2: Entry 16 of 18 File: USPT Nov 23, 1993

DOCUMENT-IDENTIFIER: US 5263940 A
TITLE: Fluid dispenser

Brief Summary Text (6):
Another type of balloon type infusion device is disclosed in U.S. Pat. No. 4,386,929 issued to Perry, et al. The Perry, et al. device has spaced apart inlet and outlet means and the bladder which is capable of expanding and contracting radially and axially upon inflation and deflation. When deflated the lumen of the bladder is substantially completely filled by lumen filling means which protect the bladder from being punctured by the hypodermic needle used to fill and inflate the bladder. The lumen filling means resists the compressive load applied during insertion of the needle and maintains the inlet and outlet means in spaced apart relationship while providing substantially no resistance to the axial expansion of the bladder. By having the lumen of the bladder filled with the lumen filling means when the bladder is deflated, before its subsequent inflation and deflation, substantially complete expulsion of the fluid contents of the bladder can be obtained.

Detailed Description Text (17):
Biologically Active Material--a substance which is biochemically, immunochemically, physiologically, or pharmaceutically active or reactive. Biologically active material includes at least one or more of the following: biochemical compounds (such as amio acids, carbohydrates, lipids, nucleic acids, proteins, and other biochemicals and substances which may complex or interact with biochemical compounds), such biochemical compounds biologically functioning as . antibodies, antigenic substances, enzymes, co-factors, inhibitors, lectins, hormones, hormone producting cells, receptors, coagulation factors, anti-fungal agents, growth enhancers, histones, peptides, vitamins, drugs, cell surface markers and toxins, among others known to those skilled in the art. Of the group of biologically active materials described, proteins are of utmost current interest because of the large molecule genetically engineered bio-pharmaceuticals as those species to be immobilized on the additive carriers hereinafter to be described. A discussion of the use of biomosaic polymers as carriers for biologically active materials is set forth in European Patent Application 0,430,517 A2.

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File 370:Science 1996-1999/Jul W3
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***File 370: This file is closed (no updates). Use File 47 for more current**
information.
File 399:CA SEARCH(R) 1967-2005/UD=14319
(c) 2005 American Chemical Society
***File 399: Use is subject to the terms of your user/customer agreement.**
Alert feature enhanced for multiple files, etc. See HELP ALERT.
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
(c) 1998 Inst for Sci Info
File 444:New England Journal of Med. 1985-2005/Oct W3
(c) 2005 Mass. Med. Soc.
File 467:ExtraMED(tm) 2000/Dec
(c) 2001 Informania Ltd.
***File 467: F467 no longer updates; see Help News467.**

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      Set  Items  Description
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?

Ref   Items   RT  Index-term
E1        5       BOTULINUM INJECTION
E2        0    1  BOTULINUM INTOXICATION
E3      353    1 *BOTULINUM NEUROTOXIN
E4       92    1  BOTULINUM NEUROTOXIN A
E5        2       BOTULINUM NEUROTOXIN A (BONT/A)
E6        1       BOTULINUM NEUROTOXIN A ANTIBODIES
E7        1       BOTULINUM NEUROTOXIN A BONT-A
E8        1       BOTULINUM NEUROTOXIN A BONT/A DYSPORT
E9        1       BOTULINUM NEUROTOXIN A BOTOX
E10       1       BOTULINUM NEUROTOXIN A C-TERMINAL FRAGMENT
E11       1       BOTULINUM NEUROTOXIN A DYSPORT
E12       1       BOTULINUM NEUROTOXIN A ENDOPEPTIDASE

          Enter P or PAGE for more
?
? p

Ref   Items  Index-term
E13       1  BOTULINUM NEUROTOXIN A GENE
E14       1  BOTULINUM NEUROTOXIN A HEAVY CHAIN
E15       1  BOTULINUM NEUROTOXIN A INHIBITOR
E16       1  BOTULINUM NEUROTOXIN A INHIBITORS
E17       1  BOTULINUM NEUROTOXIN A TYPE
E18       1  BOTULINUM NEUROTOXIN A/B PROTEASE INHIBITORS
E19       1  BOTULINUM NEUROTOXIN ANTAGONISTS
E20       1  BOTULINUM NEUROTOXIN ANTIBODIES
E21       1  BOTULINUM NEUROTOXIN AUTOCATALYSIS
E22      36  BOTULINUM NEUROTOXIN B
E23       1  BOTULINUM NEUROTOXIN B BONT/B
E24       1  BOTULINUM NEUROTOXIN B GENE

          Enter P or PAGE for more
? s e4-425
>>>Term "425" in invalid position
? s e4-e35
              92  BOTULINUM NEUROTOXIN A
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               1  BOTULINUM NEUROTOXIN A BONT-A
               1  BOTULINUM NEUROTOXIN A BONT/A DYSPORT
               1  BOTULINUM NEUROTOXIN A BOTOX
               1  BOTULINUM NEUROTOXIN A C-TERMINAL FRAGMENT
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               1  BOTULINUM NEUROTOXIN A ENDOPEPTIDASE
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               1  BOTULINUM NEUROTOXIN A HEAVY CHAIN
               1  BOTULINUM NEUROTOXIN A INHIBITOR
               1  BOTULINUM NEUROTOXIN A INHIBITORS
               1  BOTULINUM NEUROTOXIN A TYPE
               1  BOTULINUM NEUROTOXIN A/B PROTEASE INHIBITORS
               1  BOTULINUM NEUROTOXIN ANTAGONISTS
               1  BOTULINUM NEUROTOXIN ANTIBODIES
               1  BOTULINUM NEUROTOXIN AUTOCATALYSIS
              36  BOTULINUM NEUROTOXIN B
               1  BOTULINUM NEUROTOXIN B BONT/B
               1  BOTULINUM NEUROTOXIN B GENE
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                1  BOTULINUM NEUROTOXIN B INHIBITOR
                1  BOTULINUM NEUROTOXIN B LIGHT CHAIN
                1  BOTULINUM NEUROTOXIN B LIGHT CHAIN INHIBITOR
                1  BOTULINUM NEUROTOXIN B NEUROBLOC
                1  BOTULINUM NEUROTOXIN B TYPE
                2  BOTULINUM NEUROTOXIN BONT
               14  BOTULINUM NEUROTOXIN C
                2  BOTULINUM NEUROTOXIN C-6813
                1  BOTULINUM NEUROTOXIN CELL SURFACE RECEPTORS
                8  BOTULINUM NEUROTOXIN COMPLEX
                1  BOTULINUM NEUROTOXIN COMPLEX NONTOXIC-NONHEMAG
      S1      153  E4-E35
? s neurotoxin?
      S2   104285  NEUROTOXIN?
? s bladder? (3n) lumen?
           510574  BLADDER?
           184092  LUMEN?
      S3      905  BLADDER? (3N) LUMEN?
? ds

Set     Items   Description
S1        153   E4-E35
S2     104285   NEUROTOXIN?
S3        905   BLADDER? (3N) LUMEN?
? s (s1 or s2) (100n) s3
              153  S1
           104285  S2
              905  S3
      S4        0  (S1 OR S2) (100N) S3
? s intravesic?
      S5    35756  INTRAVESIC?
? s s5 (5n) bladder?
            35756  S5
           510574  BLADDER?
      S6    11424  S5 (5N) BLADDER?
? s s6 (100n) (s1 or s2)
            11424  S6
              153  S1
           104285  S2
      S7       26  S6 (100N) (S1 OR S2)
? s s7/2003:2005
Processing
Processed  10 of  26 files ...
>>>One or more prefixes are unsupported
>>>  or undefined in one or more files.
>>>Year ranges not supported in one or more files
Completed processing all files
               26  S7
         14444054  PY=2003 : PY=2005
      S8        8  S7/2003:2005
? s s7 not s8
               26  S7
                8  S8
      S9       18  S7 NOT S8
? target s9/all
Your TARGET search request will retrieve up to 50 of the statistically most
relevant records.
Searching ALL records
...Processed 10   out of 26  files
...Processed 20   out of 26  files
...Processing Complete
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S10 18 TARGET - S9
Ending TARGET search. Enter TARGET to do another search in the present file(s), or BEGIN new file(s). Enter LOGOFF to disconnect from Dialog
?
? rd
>>>Set 10 has been sorted, and cannot be processed further.
? t s10/6/all

10/6/1 (Item 1 from file: 5)
0012937214 BIOSIS NO.: 200100109053
The role of bladder afferent pathways in the bladder hyperactivity induced by intravesical administration of nerve growth factor
2000

10/6/2 (Item 2 from file: 155)
12514013 PMID: 9825395
Intravesical resiniferatoxin for the treatment of detrusor hyperreflexia refractory to capsaicin in patients with chronic spinal cord diseases.
Sep 1998

10/6/3 (Item 3 from file: 156)
3355507 NLM Doc No: 9825395
Intravesical resiniferatoxin for the treatment of detrusor hyperreflexia refractory to capsaicin in patients with chronic spinal cord diseases.
Sep 1998

10/6/4 (Item 4 from file: 155)
12998096 PMID: 10953167
CNS induced neurogenic cystitis is associated with bladder mast cell degranulation in the rat.
Sep 2000

10/6/5 (Item 5 from file: 156)
3426006 NLM Doc No: 10953167
CNS induced neurogenic cystitis is associated with bladder mast cell degranulation in the rat.
Sep 2000

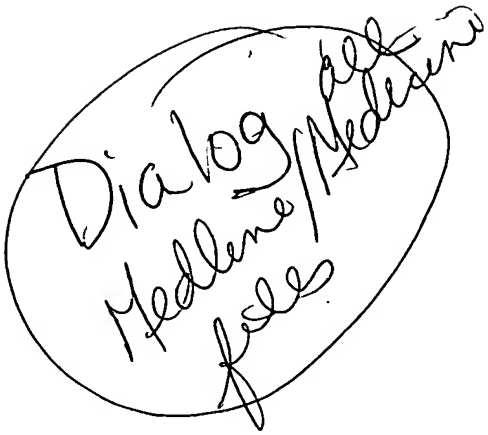
10/6/6 (Item 6 from file: 34)
08912990 Genuine Article#: 343BP Number of References: 40
Title: Botulinum-a toxin for treating detrusor hyperreflexia in spinal cord injured patients: A new alternative to anticholinergic drugs? Preliminary results (ABSTRACT AVAILABLE)
Publication date: 20000900

10/6/7 (Item 7 from file: 34)
08140537 Genuine Article#: 250YE Number of References: 54
Title: Intravesical instillations of capsaicin in urology: from pharmacological principles to therapeutic applications. (ABSTRACT AVAILABLE)
Publication date: 19990900

10/6/8 (Item 8 from file: 155)

12637259 PMID: 10555213
[Intravesical instillations of capsaicin in urology: from pharmacological principles to therapeutic applications]
Instillations intravesicales de capsaicine en urologie. Des principes pharmacologiques aux applications therapeutiques.
Sep 1999

10/6/9 (Item 9 from file: 155)
11033827 PMID: 7609147
Urodynamic effects of intravesical resiniferatoxin and capsaicin in conscious rats with and without outflow obstruction.
Aug 1995

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et      Items   Description
S1        153   E4-E35
S2     104285   NEUROTOXIN?
S3        905   BLADDER? (3N) LUMEN?
S4          0   (S1 OR S2) (100N) S3
S5      35756   INTRAVESIC?
S6      11424   S5 (5N) BLADDER?
S7         26   S6 (100N) (S1 OR S2)
S8          8   S7/2003:2005
S9         18   S7 NOT S8
S10        18   TARGET - S9
S11      1342   'LUMEN'
S12        10   'LUMEN CATHETER'
S13         5   'LUMEN CATHETERS'
S14         4   'DETRUSOR SPHINCTER SYNERGIA' OR 'DETRUSOR SPHINCTER-DYSSY-
                NERGIA'
S15         5   'DETRUSOR BLADDER NECK DYSSYNERGIA' OR 'DETRUSOR BLADDER C-
                ATHETER AGE PARITY'
S16         1   'DETRUSOR CONTRACTILE DYSFUNCTION'
S17         1   'DETRUSOR CONTRACTION CONTROL'
S18         3   'DETRUSOR CONTRACTION INHIBITION'
S19         6   'DETRUSOR CONTRACTION VESICAL NECK INCISION URI' OR 'DETRU-
                SOR CONTRACTIONS'
S20         1   'DETRUSOR CONTRACTIONS CYSTOMETRY DRUG THERAPY'
S21        23   'DETRUSOR DYSFUNCTION'
S22     20529   R1-R8
S23       417   'DETRUSOR DYSSYNERGIA --DRUG THERAPY --DT'
S24         1   'DETRUSOR HYPERREFLEXIA UNSTABLE URETHRA'
S25       466   'DETRUSOR HYPERREFLEXIA'
S26         1   'DETRUSOR IMPLANTATION'
S27         9   E14-E18
? s s14 or s15 or s16 or s17 ot s18 or s19 or s20 or s21 or s22 or s23 or s24
or s25 or s26 or s27
>>>Term "OT" in invalid position
? s s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24
or s25 or s26 or s27
                4  S14
                5  S15
                1  S16
                1  S17
                3  S18
                6  S19
                1  S20
               23  S21
            20529  S22
              417  S23
                1  S24
              466  S25
                1  S26
                9  S27
     S28    21018  S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR
                   S22 OR S23 OR S24 OR S25 OR S26 OR S27
? ds

Set     Items   Description
S1        153   E4-E35
S2     104285   NEUROTOXIN?
S3        905   BLADDER? (3N) LUMEN?
S4          0   (S1 OR S2) (100N) S3
S5      35756   INTRAVESIC?
S6      11424   S5 (5N) BLADDER?
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S7          26   S6 (100N) (S1 OR S2)
S8           8   S7/2003:2005
S9          18   S7 NOT S8
S10         18   TARGET - S9
S11       1342   'LUMEN'
S12         10   'LUMEN CATHETER'
S13          5   'LUMEN CATHETERS'
S14          4   'DETRUSOR SPHINCTER SYNERGIA' OR 'DETRUSOR SPHINCTER-DYSSY-
                 NERGIA'
S15          5   'DETRUSOR BLADDER NECK DYSSYNERGIA' OR 'DETRUSOR BLADDER C-
                 ATHETER AGE PARITY'
S16          1   'DETRUSOR CONTRACTILE DYSFUNCTION'
S17          1   'DETRUSOR CONTRACTION CONTROL'
S18          3   'DETRUSOR CONTRACTION INHIBITION'
S19          6   'DETRUSOR CONTRACTION VESICAL NECK INCISION URI' OR 'DETRU-
                 SOR CONTRACTIONS'
S20          1   'DETRUSOR CONTRACTIONS CYSTOMETRY DRUG THERAPY'
S21         23   'DETRUSOR DYSFUNCTION'
S22      20529   R1-R8
S23        417   'DETRUSOR DYSSYNERGIA --DRUG THERAPY --DT'
S24          1   'DETRUSOR HYPERREFLEXIA UNSTABLE URETHRA'
S25        466   'DETRUSOR HYPERREFLEXIA'
S26          1   'DETRUSOR IMPLANTATION'
S27          9   E14-E18
S28      21018   S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
                 OR S23 OR S24 OR S25 OR S26 OR S27
? s s28 (100n) (s1 or s2)
           21018  S28
             153  S1
          104285  S2
     S29       0  S28 (100N) (S1 OR S2)
? s s28 and toxin?
           21018  S28
          746407  TOXIN?
     S30     297  S28 AND TOXIN?
? s s30 and neurotoxin?
             297  S30
          104285  NEUROTOXIN?
     S31      13  S30 AND NEUROTOXIN?
? rd
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? s s32 not s9
              13  S32
              18  S9
     S33      13  S32 NOT S9
? s s33/2003:2005
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>>>Year ranges not supported in one or more files
              13  S33
        14444054  PY=2003 : PY=2005
     S34      11  S33/2003:2005
? s s33 not s34
              13  S33
              11  S34
     S35       2  S33 NOT S34
? t s35/6/all

 35/6/1     (Item 1 from file: 5)
0013264340   BIOSIS NO.: 200100436179
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Botulinum-A toxin in the treatment of detrusor hyperreflexia
2001

35/6/2 (Item 1 from file: 73)
07796755 EMBASE No: 1999279042
Botulinum toxin in the treatment of neurological disorders of the autonomic nervous system
1999
? logoff hold
02nov05 12:29:05 User228206 Session D2533.

detrusor (dē-troo′ser, -sōr)

1. A muscle that has the action of expelling a substance.
2. See: detrusor (muscle)

[L. *detrudo*, to drive away]

Prev

detrusor

A muscle that has the action of expelling a substance.

Origin: L. Detrudo, to drive away

(05 Mar 2000)

Previous: detoxification reaction, detoxify, detractress, detrital, detrition, detritivore, detritus
Next: detrusor compliance, detrusor hyperreflexia

dyssynergia (dis-in-er'jĕ-ă)

An aspect of ataxia, in which an act is not performed smoothly or accurately because of lack of harmonious association of its various components; usually used to describe abnormalities of movement caused by cerebellar disorders.

[dys- + G. *syn,* with, + *ergon,* work]

Prev

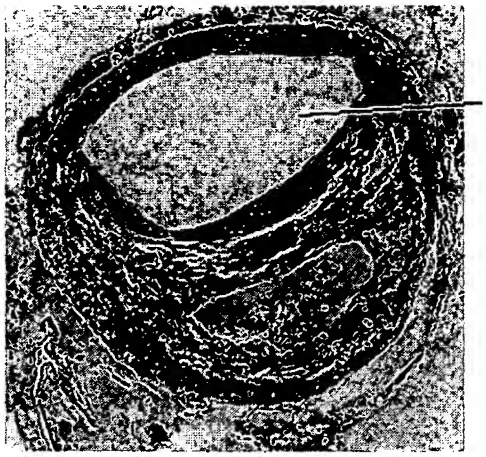
bladder

A membranous sac that serves as a reservoir for urine. Contraction of the bladder results in urination.

(27 Sep 1997)

Previous: blackwater fever, black widow spider, black widow spider venom, blackwood
Next: bladder calcification, bladder calculi, bladder cancer

lumen (lu·men) (loo′mən) pl. *lu′mina, lumens* [L. "light"] 1. the cavity or channel within a tube or tubular organ. 2. the SI unit of luminous flux; it is the light emitted in a solid angle of 1 steradian by a uniform point source with luminous intensity of 1 candela. Abbreviated lm.



lumen , pl. **lumina,** pl. **lumens** (loo′men, -min-ă, -menz)

1. The space in the interior of a tubular structure, such as an artery or the intestine.
2. (lm)The unit of luminous flux; the luminous flux emitted in a unit solid angle of 1 steradian by a uniform point source of light having a luminous intensity of 1 candela.
3. The volume enclosed within the membranes of a mitochondrion or of the endoplasmic reticulum.
4. The bore of a catheter or hollow needle.

[L. light, window]

Prev

: Chuang YC, Fraser MO, Yu Y, Chancellor MB, de Groat WC, Yoshimura N. Related Articles, Links

The role of bladder afferent pathways in bladder hyperactivity induced by the intravesical administration of nerve growth factor.
J Urol. 2001 Mar;165(3):975-9.
PMID: 11176525 [PubMed - indexed for MEDLINE]

☐ 54: Bustamante S, Orensanz LM, Barahona MV, Contreras J, Garcia-Sacristan A, Hernandez M. Related Articles, Links

Tachykininergic excitatory neurotransmission in the pig intravesical ureter.
J Urol. 2000 Oct;164(4):1371-5.
PMID: 10992417 [PubMed - indexed for MEDLINE]

☐ 55: Jasmin L, Janni G, Ohara PT, Rabkin SD. Related Articles, Links

CNS induced neurogenic cystitis is associated with bladder mast cell degranulation in the rat.
J Urol. 2000 Sep;164(3 Pt 1):852-5.
PMID: 10953167 [PubMed - indexed for MEDLINE]

☐ 56: Lazzeri M, Beneforti P, Spinelli M, Zanollo A, Barbagli G, Turini D. Related Articles, Links

Intravesical resiniferatoxin for the treatment of hypersensitive disorder: a randomized placebo controlled study.
J Urol. 2000 Sep;164(3 Pt 1):676-9.
PMID: 10953124 [PubMed - indexed for MEDLINE]

☐ 57: Fowler CJ. Related Articles, Links

Intravesical treatment of overactive bladder.
Urology. 2000 May;55(5A Suppl):60-4; discussion 66. Review.
PMID: 10767456 [PubMed - indexed for MEDLINE]

☐ 58: Kim DY, Chancellor MB. Related Articles, Links

Intravesical neuromodulatory drugs: capsaicin and resiniferatoxin to treat the overactive bladder.
J Endourol. 2000 Feb;14(1):97-103. Review.
PMID: 10735579 [PubMed - indexed for MEDLINE]

☐ 59: de Seze M, Wiart L, Ferriere JM, de Seze MP, Joseph PA, Barat M. Related Articles, Links

[Intravesical instillations of capsaicin in urology: from pharmacological principles to therapeutic applications]
Prog Urol. 1999 Sep;9(4):615-32. Review. French.
PMID: 10555213 [PubMed - indexed for MEDLINE]

☐ 60: Avelino A, Cruz F, Coimbra A. Related Articles, Links

Intravesical resiniferatoxin desensitizes rat bladder sensory fibres without causing intense noxious excitation. A c-fos study.
Eur J Pharmacol. 1999 Jul 28;378(1):17-22.
PMID: 10478560 [PubMed - indexed for MEDLINE]

☐ 61: Yu Y, de Groat WC. Related Articles, Links

Effects of ZD6169, a K(ATP) channel opener, on the micturition reflex in the rat.
J Pharmacol Exp Ther. 1999 Aug;290(2):825-31.
PMID: 10411598 [PubMed - indexed for MEDLINE]

☐ 62: Chancellor MB, de Groat WC. Related Articles, Links

Intravesical capsaicin and resiniferatoxin therapy: spicing up the ways to treat the

overactive bladder.
J Urol. 1999 Jul;162(1):3-11. Review.
PMID: 10379728 [PubMed - indexed for MEDLINE]

☐ **63:** Komiyama I, Igawa Y, Ishizuka O, Nishizawa O, Andersson KE. Related Articles, Links

Effects of intravesical capsaicin and resiniferatoxin on distension-induced bladder contraction in conscious rats with and without chronic spinal cord injury.
J Urol. 1999 Jan;161(1):314-9.
PMID: 10037430 [PubMed - indexed for MEDLINE]

☐ **64:** Lazzeri M, Spinelli M, Beneforti P, Zanollo A, Turini D. Related Articles, Links

Intravesical resiniferatoxin for the treatment of detrusor hyperreflexia refractory to capsaicin in patients with chronic spinal cord diseases.
Scand J Urol Nephrol. 1998 Sep;32(5):331-4.
PMID: 9825395 [PubMed - indexed for MEDLINE]

☐ **65:** Cruz F. Related Articles, Links

Desensitization of bladder sensory fibers by intravesical capsaicin or capsaicin analogs. A new strategy for treatment of urge incontinence in patients with spinal detrusor hyperreflexia or bladder hypersensitivity disorders.
Int Urogynecol J Pelvic Floor Dysfunct. 1998;9(4):214-20. Review.
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☐ **66:** de Seze M, Wiart L, Joseph PA, Dosque JP, Mazaux JM, Barat M. Related Articles, Links

Capsaicin and neurogenic detrusor hyperreflexia: a double-blind placebo-controlled study in 20 patients with spinal cord lesions.
Neurourol Urodyn. 1998;17(5):513-23.
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☐ **67:** Lazzeri M, Beneforti P, Turini D. Related Articles, Links

Urodynamic effects of intravesical resiniferatoxin in humans: preliminary results in stable and unstable detrusor.
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☐ **68:** Cruz F, Guimaraes M, Silva C, Reis M. Related Articles, Links

Suppression of bladder hyperreflexia by intravesical resiniferatoxin.
Lancet. 1997 Aug 30;350(9078):640-1. No abstract available.
PMID: 9288055 [PubMed - indexed for MEDLINE]

☐ **69:** Ishizuka O, Mattiasson A, Andersson KE. Related Articles, Links

Urodynamic effects of intravesical resiniferatoxin and capsaicin in conscious rats with and without outflow obstruction.
J Urol. 1995 Aug;154(2 Pt 1):611-6.
PMID: 7609147 [PubMed - indexed for MEDLINE]

☐ **70:** Craft RM, Porreca F. Related Articles, Links

Temporal parameters of desensitization to intravesical resiniferatoxin in the rat.
Physiol Behav. 1994 Sep;56(3):479-85.
PMID: 7972397 [PubMed - indexed for MEDLINE]

☐ **71:** Craft RM, Porreca F. Related Articles, Links

Tetracaine attenuates irritancy without attenuating desensitization produced by intravesical resiniferatoxin in the rat.

Pain. 1994 Jun;57(3):351-9.
PMID: 7936713 [PubMed - indexed for MEDLINE]

factor (0.5 ml. of 20 mug./ml. in 10% dimethyl sulfoxide) or a vehicle solution (0.5 ml. of 10% dimethyl sulfoxide) was infused into the bladder through a transurethral catheter and retained for 1 hour. Results: In Wistar rats nerve growth factor increased the mean number of contractions by 111% versus controls (5.7 versus 2.7, p <0.05), and decreased the mean volume threshold by 41% (0.244 versus 0.412 ml., p <0.05). This effect of nerve growth factor was not detected in Sprague-Dawley rats. Capsaicin pretreatment increased the volume threshold by 59% but did not change nerve growth factor induced bladder hyperactivity. Conclusions: The intravesical application of nerve growth factor acutely induced bladder hyperactivity in Wistar but not in Sprague-Dawley rats. Because the C fiber afferent neurotoxin capsaicin did not change the effect of nerve growth factor, we believe that Adelta afferent neurons have a major role in nerve growth factor induced bladder hyperactivity.

DRUG DESCRIPTORS:
*nerve growth factor
capsaicin
MEDICAL DESCRIPTORS:
*sensory nerve; *bladder dysfunction
hyperactivity; interstitial cystitis; bladder contraction; urine volume; micturition; desensitization; pain; nonhuman; female; rat; animal experiment; animal model; controlled study; article; priority journal
CAS REGISTRY NO.: 9061-61-4 (nerve growth factor); 404-86-4 (capsaicin)
SECTION HEADINGS:
028 Urology and Nephrology

10/9/14 (Item 14 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09406627 Genuine Article#: 401AT Number of References: 20
Title: The role of bladder afferent pathways in bladder hyperactivity induced by the intravesical administration of nerve growth factor
Author(s): Chuang YC (REPRINT) ; Fraser MO; Yu YB; Chancellor MB; de Groat WC; Yoshimura N
Corporate Source: Chang Gung Mem Hosp,Div Urol,123 Ta Pei Rd/Kaohsiung//Taiwan/ (REPRINT); Chang Gung Mem Hosp,Div Urol,Kaohsiung//Taiwan/; Univ Pittsburgh,Sch Med, Dept Pharmacol,Pittsburgh//PA/15261; Univ Pittsburgh,Sch Med, Dept Urol,Pittsburgh//PA/; Natl Yang Ming Univ,Sch Med, Dept Urol,Taipei 112//Taiwan/
Journal: JOURNAL OF UROLOGY, 2001, V165, N3 (MAR), P975-979
ISSN: 0022-5347 Publication date: 20010300
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA
Language: English Document Type: ARTICLE
Geographic Location: Taiwan; USA
Journal Subject Category: UROLOGY & NEPHROLOGY
Abstract: Purpose: Interstitial cystitis, a chronic disease of the bladder, is characterized by urinary frequency, urgency and suprapubic pain. Nerve growth factor is a substance that may sensitize afferent nerves and induce bladder hyperactivity. It is often increased in the urine of patients with interstitial cystitis. We evaluated the role of A delta and C fiber afferents in the type of bladder hyperactivity induced by the intravesical administration of nerve growth factor.

Materials and Methods: A total of 22 Wistar and 8 Sprague-Dawley adult female rats were anesthetized with 1.2 gm./kg. urethane given subcutaneously. A transurethral catheter was inserted into the bladder.

Some animals were pretreated with 125 mg./kg. capsaicin injected subcutaneously 4 days before nerve growth factor administration. Cystometry was performed by slowly filling the bladder at a rate of 0.04 ml. per minute for 15 minutes with a volume of up to 0.6 ml. Parameters measured included volume threshold and pressure threshold for inducing the micturition reflex, compliance, bladder contraction amplitude, number of contractions and the inter-contraction interval. Nerve growth factor (0.5 ml. of 20 mug./ml. in 10% dimethyl sulfoxide) or a vehicle solution (0.5 ml. of 10% dimethyl sulfoxide) was infused into the bladder through a transurethral catheter and retained for 1 hour.

Results: In Wistar rats nerve growth factor increased the mean number of contractions by 111% versus controls (5.7 versus 2.7, p <0.05), and decreased the mean volume threshold by 41% (0.244 versus 0.412 ml., p <0.05). This effect of nerve growth factor was not detected in Sprague-Dawley rats. Capsaicin pretreatment increased the volume threshold by 59% but did not change nerve growth factor induced bladder hyperactivity.

Conclusions: The **intravesical** application of nerve growth factor acutely induced bladder hyperactivity in Wistar but not in Sprague-Dawley rats. Because the C fiber afferent **neurotoxin** capsaicin did not change the effect of nerve growth factor, we believe that A delta afferent neurons have a major role in nerve growth factor induced bladder hyperactivity.

Descriptors--Author Keywords: bladder ; nerve growth factor ; capsaicin ; afferent pathways ; rats, Wistar

Identifiers--KeyWord Plus(R): IDIOPATHIC SENSORY URGENCY; INTERSTITIAL CYSTITIS; SPRAGUE-DAWLEY; WISTAR RATS; MICTURITION; INNERVATION; REFLEXES; WOMEN

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10/9/15 (Item 15 from file: 71)

01673260 2001045239

The role of bladder afferent pathways in bladder hyperactivity induced by the intravesical administration of nerve growth factor

Chuang Y.-C.; Fraser M.O.; Yu Y.; Chancellor M.B.; De Groat W.C.; Yoshimura N.
ADDRESS: Y.-C. Chuang, Division of Urology, Chang Gung Memorial Hospital, 123 Ta-pei Road, Niao-Sung Hsiang, Kaohsiung, Taiwan
Journal: Journal of Urology, 165/3 (975-979), 2001, United States
CODEN: JOURA
ISSN: 0022-5347
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 20

Purpose: Interstitial cystitis, a chronic disease of the bladder, is characterized by urinary frequency, urgency and suprapubic pain. Nerve growth factor is a substance that may sensitize afferent nerves and induce bladder hyperactivity. It is often increased in the urine of patients with interstitial cystitis. We evaluated the role of Adelta and C fiber afferents in the type of bladder hyperactivity induced by the intravesical administration of nerve growth factor. Materials and Methods: A total of 22 Wistar and 8 Sprague-Dawley adult female rats were anesthetized with 1.2 gm./kg. urethane given subcutaneously. A transurethral catheter was inserted into the bladder. Some animals were pretreated with 125 mg./kg. capsaicin injected subcutaneously 4 days before nerve growth factor administration. Cystometry was performed by slowly filling the bladder at a rate of 0.04 ml. per minute for 15 minutes with a volume of up to 0.6 ml. Parameters measured included volume threshold and pressure threshold for inducing the micturition reflex, compliance, bladder contraction amplitude, number of contractions and the inter-contraction interval. Nerve growth factor (0.5 ml. of 20 mug./ml. in 10% dimethyl sulfoxide) or a vehicle solution (0.5 ml. of 10% dimethyl sulfoxide) was infused into the bladder through a transurethral catheter and retained for 1 hour. Results: In Wistar rats nerve growth factor increased the mean number of contractions by 111% versus controls (5.7 versus 2.7, $p < 0.05$), and decreased the mean volume threshold by 41% (0.244 versus 0.412 ml., $p < 0.05$). This effect of nerve growth factor was not detected in Sprague-Dawley rats. Capsaicin pretreatment increased the volume threshold by 59% but did not change nerve growth factor induced bladder hyperactivity. Conclusions: The **intravesical** application of nerve growth factor acutely induced bladder hyperactivity in Wistar but not in Sprague-Dawley rats. Because the C fiber afferent **neurotoxin** capsaicin did not change the effect of nerve growth factor, we believe that Adelta afferent neurons have a major role in nerve growth factor induced bladder hyperactivity.

DESCRIPTORS:
Bladder; nerve growth factor; capsaicin; afferent pathways; Rats, Wistar

CLASSIFICATION CODE AND DESCRIPTION:
83.6.17 - ENDOCRINOLOGY AND METABOLISM / ENDOCRINE SYSTEMS / Growth Factors
83.7.8 - ENDOCRINOLOGY AND METABOLISM / METABOLIC REGULATION IN SPECIFIC ORGAN SITES / Renal System

10/9/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012981106 BIOSIS NO.: 200100152945
The role of bladder afferent pathways in bladder hyperactivity induced by the intravesical administration of nerve growth factor
AUTHOR: Chuang Yao-Chi (Reprint); Fraser Matthew O; Yu Yongbei; Chancellor Michael B; de Groat William C; Yoshimura Naoki
AUTHOR ADDRESS: Division of Urology, Chang Gung Memorial Hospital, 123

Ta-pei Road, Niao-Sung Hsiang, Kaohsiung, Taiwan**Taiwan
JOURNAL: Journal of Urology 165 (3): p975-979 March, 2001 2001
MEDIUM: print
ISSN: 0022-5347
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose: Interstitial cystitis, a chronic disease of the bladder, is characterized by urinary frequency, urgency and suprapubic pain. Nerve growth factor is a substance that may sensitize afferent nerves and induce bladder hyperactivity. It is often increased in the urine of patients with interstitial cystitis. We evaluated the role of Adelta and C fiber afferents in the type of bladder hyperactivity induced by the intravesical administration of nerve growth factor. Materials and Methods: A total of 22 Wistar and 8 Sprague-Dawley adult female rats were anesthetized with 1.2 gm./kg. urethane given subcutaneously. A transurethral catheter was inserted into the bladder. Some animals were pretreated with 125 mg./kg. capsaicin injected subcutaneously 4 days before nerve growth factor administration. Cystometry was performed by slowly filling the bladder at a rate of 0.04 ml. per minute for 15 minutes with a volume of up to 0.6 ml. Parameters measured included volume threshold and pressure threshold for inducing the micturition reflex, compliance, bladder contraction amplitude, number of contractions and the inter-contraction interval. Nerve growth factor (0.5 ml. of 20 mug./ml. in 10% dimethyl sulfoxide) or a vehicle solution (0.5 ml. of 10% dimethyl sulfoxide) was infused into the bladder through a transurethral catheter and retained for 1 hour. Results: In Wistar rats nerve growth factor increased the mean number of contractions by 111% versus controls (5.7 versus 2.7, $p < 0.05$), and decreased the mean volume threshold by 41% (0.244 versus 0.412 ml., $p < 0.05$). This effect of nerve growth factor was not detected in Sprague-Dawley rats. Capsaicin pretreatment increased the volume threshold by 59% but did not change nerve growth factor induced bladder hyperactivity. Conclusions: The **intravesical** application of nerve growth factor acutely induced bladder hyperactivity in Wistar but not in Sprague-Dawley rats. Because the C fiber afferent **neurotoxin** capsaicin did not change the effect of nerve growth factor, we believe that Adelta afferent neurons have a major role in nerve growth factor induced bladder hyperactivity.

REGISTRY NUMBERS: 9061-61-4: nerve growth factor
DESCRIPTORS:
MAJOR CONCEPTS: Urinary System--Chemical Coordination and Homeostasis; Nervous System--Neural Coordination
BIOSYSTEMATIC NAMES: Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: rat (Muridae)
ORGANISMS: PARTS ETC: afferent nerves--nervous system; bladder afferent pathways--excretory system, nervous system
COMMON TAXONOMIC TERMS: Animals; Chordates; Mammals; Nonhuman Vertebrates ; Nonhuman Mammals; Rodents; Vertebrates
DISEASES: bladder hyperactivity--urologic disease; interstitial cystitis --urologic disease
MESH TERMS: Cystitis, Interstitial (MeSH)
CHEMICALS & BIOCHEMICALS: nerve growth factor--intravesical administration
METHODS & EQUIPMENT: cystometry--analytical method
MISCELLANEOUS TERMS: micturition reflex; pressure threshold; volume threshold
CONCEPT CODES:
15504 Urinary system - Physiology and biochemistry

10064 Biochemistry studies - Proteins, peptides and amino acids
15506 Urinary system - Pathology
17020 Endocrine - Neuroendocrinology
20504 Nervous system - Physiology and biochemistry
BIOSYSTEMATIC CODES:
86375 Muridae

10/9/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13595443 PMID: 11176525
The role of bladder afferent pathways in bladder hyperactivity induced by the intravesical administration of nerve growth factor.
Chuang Y C; Fraser M O; Yu Y; Chancellor M B; de Groat W C; Yoshimura N
Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.
Journal of urology (United States) Mar 2001, 165 (3) p975-9, ISSN 0022-5347 Journal Code: 0376374
Contract/Grant No.: DK 49430; DK; NIDDK; DK 57267; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: AIM; INDEX MEDICUS
PURPOSE: Interstitial cystitis, a chronic disease of the bladder, is characterized by urinary frequency, urgency and suprapubic pain. Nerve growth factor is a substance that may sensitize afferent nerves and induce bladder hyperactivity. It is often increased in the urine of patients with interstitial cystitis. We evaluated the role of Adelta and C fiber afferents in the type of bladder hyperactivity induced by the intravesical administration of nerve growth factor. MATERIALS AND METHODS: A total of 22 Wistar and 8 Sprague-Dawley adult female rats were anesthetized with 1.2 gm/kg urethane given subcutaneously. A transurethral catheter was inserted into the bladder. Some animals were pretreated with 125 mg/kg capsaicin injected subcutaneously 4 days before nerve growth factor administration. Cystometry was performed by slowly filling the bladder at a rate of 0.04 ml per minute for 15 minutes with a volume of up to 0.6 ml. Parameters measured included volume threshold and pressure threshold for inducing the micturition reflex, compliance, bladder contraction amplitude, number of contractions and the inter-contraction interval. Nerve growth factor (0.5 ml of 20 microg/ml in 10% dimethyl sulfoxide) or a vehicle solution (0.5 ml of 10% dimethyl sulfoxide) was infused into the bladder through a transurethral catheter and retained for 1 hour. RESULTS: In Wistar rats nerve growth factor increased the mean number of contractions by 111% versus controls (5.7 versus 2.7, $p < 0.05$), and decreased the mean volume threshold by 41% (0.244 versus 0.412 ml, $p < 0.05$). This effect of nerve growth factor was not detected in Sprague-Dawley rats. Capsaicin pretreatment increased the volume threshold by 59% but did not change nerve growth factor induced bladder hyperactivity. CONCLUSIONS: The **intravesical** application of nerve growth factor acutely induced bladder hyperactivity in Wistar but not in Sprague-Dawley rats. Because the C fiber afferent **neurotoxin** capsaicin did not change the effect of nerve growth factor, we believe that Adelta afferent neurons have a major role in nerve growth factor induced bladder hyperactivity.
Tags: Female; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.
Descriptors: *Afferent Pathways--drug effects--DE; *Bladder--drug effects --DE; *Bladder--innervation--IR; *Nerve Growth Factor--administration and

--DE; *Bladder--innervation--IR; *Nerve Growth Factor--administration and dosage--AD; Administration, Intravesical; Afferent Pathways--physiology--PH ; Animals; Bladder--physiopathology--PP; Capsaicin--pharmacology--PD; Nerve Growth Factor--physiology--PH; Rats; Rats, Sprague-Dawley; Rats, Wistar

CAS Registry No.: 404-86-4 (Capsaicin); 9061-61-4 (Nerve Growth Factor)

Record Date Created: 20010222

Record Date Completed: 20010503

10/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012937214 BIOSIS NO.: 200100109053
The role of bladder afferent pathways in the bladder hyperactivity induced by intravesical administration of nerve growth factor
AUTHOR: Chuang Y C (Reprint); Fraser M O; Yu Y; Chancellor M B; de Groat W C; Yokoyama O; Yoshimura N
AUTHOR ADDRESS: University of Pittsburgh School of Medicine, Pittsburgh, PA, USA**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2): pAbstract No.-633.8 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000; 20001104
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Interstitial cystitis (IC), a chronic disease of the urinary bladder, is characterized by urinary frequency, urgency, and suprapubic pain. The urine of IC patients often exhibits increased levels of nerve growth factor (NGF), a substance that can sensitize afferent nerves and induce bladder hyperactivity. This study was conducted to examine the role of Adelta- and C-fiber afferents in the bladder hyperactivity induced by intravesical administration of NGF. Adult female rats (22 Wistar, 8 Sprague-Dawley) were anesthetized with urethane (1.2g/kg, sc) and a transurethral catheter was inserted into the bladder. Some animals were pretreated with capsaicin (125 mg/kg, sc) four days before the administration of NGF. Cystometrograms were performed by slow filling of the bladder (0.04 ml/min) for 15 min with volumes ranging up to 0.6 ml. Parameters measured included volume threshold (VT) and pressure threshold (PT) for inducing the micturition reflex, compliance, amplitude of bladder contractions, contraction number (CN), and intercontraction interval (ICI). NGF (0.5 ml, 20 mug/ml in 10 % DMSO) or a vehicle solution (0.5 ml, 10 % DMSO) was injected into the bladders through a transurethral catheter and retained for 1 hour. In Wistar rats, NGF increased CN by 111 % (5.7 versus 2.7 in controls, $P<0.05$), and decreased VT by 41 % (0.244 versus 0.412 ml in controls, $P<0.05$). This effect of NGF was not detected in Sprague-Dawley rats. Capsaicin pretreatment increased VT by 59 %, but did not alter the NGF induced bladder hyperactivity. **Intravesical** application of NGF acutely induces **bladder** hyperactivity in Wistar rats, but not in Sprague-Dawley rats. Because, capsaicin, a C-fiber afferent **neurotoxin** , did not alter the effect of NGF, we conclude that Adelta afferent neurons play a major role in NGF-induced bladder hyperactivity.

REGISTRY NUMBERS: 404-86-4: capsaicin; 9061-61-4: nerve growth factor
DESCRIPTORS:
MAJOR CONCEPTS: Urinary System--Chemical Coordination and Homeostasis; Nervous System--Neural Coordination
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: human (Hominidae); Sprague-Dawley rat (Muridae); Wistar rat (Muridae)
ORGANISMS: PARTS ETC: bladder--excretory system, hyperactivity; bladder afferent nerve--nervous system

COMMON TAXONOMIC TERMS: Humans; Primates; Animals; Chordates; Mammals; Nonhuman Vertebrates; Nonhuman Mammals; Rodents; Vertebrates
DISEASES: interstitial cystitis--urologic disease
MESH TERMS: Cystitis, Interstitial (MeSH)
CHEMICALS & BIOCHEMICALS: capsaicin; nerve growth factor--intravesical administration
MISCELLANEOUS TERMS: Meeting Abstract; Meeting Abstract
CONCEPT CODES:
15504 Urinary system - Physiology and biochemistry
00520 General biology - Symposia, transactions and proceedings
10060 Biochemistry studies - General
10064 Biochemistry studies - Proteins, peptides and amino acids
15506 Urinary system - Pathology
17020 Endocrine - Neuroendocrinology
20504 Nervous system - Physiology and biochemistry
BIOSYSTEMATIC CODES:
86215 Hominidae
86375 Muridae

10/9/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12514013 PMID: 9825395
Intravesical resiniferatoxin for the treatment of detrusor hyperreflexia refractory to capsaicin in patients with chronic spinal cord diseases.
Lazzeri M; Spinelli M; Beneforti P; Zanollo A; Turini D
Department of Urology, University of Ferrara, Italy.
Scandinavian journal of urology and nephrology (SWEDEN) Sep 1998, 32 (5) p331-4, ISSN 0036-5599 Journal Code: 0114501
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
OBJECTIVE: Resiniferatoxin (RTX), a substance isolated from some species of Euphorbia, a cactus-like plant, shows pharmacological effects similar to those of capsaicin. We have studied the possibility of treating detrusor hyperreflexia refractory to intravesical capsaicin in patients with chronic spinal cord injuries, thereby providing insight into the mechanism of action of RTX on sensory neurons and its possible future pharmacological and clinical use. MATERIALS AND METHODS: RTX saline solution (30 ml at a concentration of 10(-5) M) was instilled into the bladder of 7 patients with detrusor hyperreflexia, refractory to intravesical capsaicin therapy, and left in place for 30 min. Effects on bladder function were monitored during the treatment and at follow-up (15 days and 4 weeks later). RESULTS: Fifteen days after RTX, the mean cystomanometric capacity increased significantly from 190 ml +/- 20 ml to 407.14 ml +/- 121.06 ($p < 0.01$), and it remained high four weeks later (421.66 +/- 74.40 $p < 0.01$). After 15 days, four patients had a pharmacologically induced detrusor areflexia. They emptied their bladders by clean intermittent catheterization. After four weeks, only two patients still had a pharmacologically induced detrusor areflexia. Clinically, three patients remained dry, and the other three reported a significant improvement in their incontinence and symptoms (frequency, urgency and nocturia). CONCLUSIONS: By interfering with sensory unmyelinated fibers, intravesical RTX seems to be a promising treatment option for selected cases of detrusor hyperreflexia. The ideal dosage and treatment interval have not yet been established, and further studies are necessary to confirm our preliminary results.

Tags: Female; Male
Descriptors: *Bladder, Neurogenic--drug therapy--DT; *Capsaicin --therapeutic use--TU; *Diterpenes--therapeutic use--TU; *Neurotoxins --therapeutic use--TU; *Spinal Cord Diseases--complications--CO; Administration, Intravesical; Adult; **Bladder** --innervation--IR; **Bladder** , Neurogenic--etiology--ET; Capsaicin--administration and dosage--AD; Diterpenes--administration and dosage--AD; Humans; **Neurotoxins** --administration and dosage--AD; Reflex, Abnormal; Time Factors; Urodynamics--drug effects--DE
CAS Registry No.: 0 (Diterpenes); 0 (Neurotoxins); 404-86-4 (Capsaicin); 57444-62-9 (resiniferatoxin)
Record Date Created: 19990209
Record Date Completed: 19990209

10/9/3 (Item 3 from file: 156)
DIALOG(R)File 156:ToxFile

3355507 NLM Doc No: 9825395
Intravesical resiniferatoxin for the treatment of detrusor hyperreflexia refractory to capsaicin in patients with chronic spinal cord diseases.
Lazzeri M; Spinelli M; Beneforti P; Zanollo A; Turini D
Department of Urology, University of Ferrara, Italy.
Journal Name: Scandinavian journal of urology and nephrology (SWEDEN)
Pub. Year: Sep 1998 32 (5) p331-4, ISSN: 0036-5599 Journal Code: 0114501
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: Toxbib ; INDEX MEDICUS
OBJECTIVE: Resiniferatoxin (RTX), a substance isolated from some species of Euphorbia, a cactus-like plant, shows pharmacological effects similar to those of capsaicin. We have studied the possibility of treating detrusor hyperreflexia refractory to intravesical capsaicin in patients with chronic spinal cord injuries, thereby providing insight into the mechanism of action of RTX on sensory neurons and its possible future pharmacological and clinical use. MATERIALS AND METHODS: RTX saline solution (30 ml at a concentration of 10(-5) M) was instilled into the bladder of 7 patients with detrusor hyperreflexia, refractory to intravesical capsaicin therapy, and left in place for 30 min. Effects on bladder function were monitored during the treatment and at follow-up (15 days and 4 weeks later). RESULTS: Fifteen days after RTX, the mean cystomanometric capacity increased significantly from 190 ml +/- 20 ml to 407.14 ml +/- 121.06 ($p < 0.01$), and it remained high four weeks later (421.66 +/- 74.40 $p < 0.01$). After 15 days, four patients had a pharmacologically induced detrusor areflexia. They emptied their bladders by clean intermittent catheterization. After four weeks, only two patients still had a pharmacologically induced detrusor areflexia. Clinically, three patients remained dry, and the other three reported a significant improvement in their incontinence and symptoms (frequency, urgency and nocturia). CONCLUSIONS: By interfering with sensory unmyelinated fibers, intravesical RTX seems to be a promising treatment option for selected cases of detrusor hyperreflexia. The ideal dosage and treatment interval have not yet been established, and further studies are necessary to confirm our preliminary results.
Tags: Female; Male
Descriptors: *Bladder, Neurogenic--drug therapy--DT; *Capsaicin --therapeutic use--TU; *Diterpenes--therapeutic use--TU; *Neurotoxins --therapeutic use--TU; *Spinal Cord Diseases--complications--CO;

Administration, Intravesical; Adult; **Bladder** --innervation--IR; **Bladder**, Neurogenic--etiology--ET; Capsaicin--administration and dosage--AD; Diterpenes--administration and dosage--AD; Humans; **Neurotoxins** --administration and dosage--AD; Reflex, Abnormal; Time Factors; Urodynamics--drug effects--DE

CAS Registry No.: 0 (Diterpenes); 0 (Neurotoxins); 404-86-4 (Capsaicin); 57444-62-9 (resiniferatoxin)

Record Date Created: 19990209

Record Date Completed: 19990209

10/9/4 (Item 4 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

12998096 PMID: 10953167

CNS induced neurogenic cystitis is associated with bladder mast cell degranulation in the rat.

Jasmin L; Janni G; Ohara P T; Rabkin S D

Departments of Neurosurgery, Cell Biology, Microbiology & Immunology, Georgetown University Medical Center, Washington, DC, USA.

Journal of urology (UNITED STATES) Sep 2000, 164 (3 Pt 1) p852-5, ISSN 0022-5347 Journal Code: 0376374

Contract/Grant No.: AR46085; AR; NIAMS

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: AIM; INDEX MEDICUS

PURPOSE: To determine if bladder mast cell degranulation is involved in the genesis of neurogenic cystitis induced by pseudorabies virus (PRV) invasion of the central nervous system (CNS). MATERIALS AND METHODS: Rats received a total of 4 x 106 plaque forming units (pfu) of PRV-Bartha in the abductor caudalis dorsalis (ACD) muscle. Granulated bladder mast cells per mm2 of bladder tissue and urine histamine content were monitored as the cystitis developed over the next few days. In a subgroup of rats, intravesical resiniferatoxin was used to remove capsaicin-sensitive sensory bladder afferents, while another subgroup was pretreated with a mast cell degranulator. RESULTS: PRV injection into the ACD muscle leads to neurogenic cystitis. Histamine levels were elevated in the urine of virus injected rats before any behavioral or microscopical signs of cystitis were present. When the cystitis became clinically manifest, urine histamine returned to control levels, and the number of granulated mast cells dropped significantly. Rats in which capsaicin-sensitive afferents had been removed did not show any signs of cystitis, or increase in urine histamine, or change in the number of granulated mast cells. Pretreatment of animals with a mast cell degranulator completely prevented the appearance of cystitis without altering the CNS disease. CONCLUSION: These results provide further evidence that mast cells are involved in neurogenic cystitis induced by changes in CNS activity.

Tags: Male; Research Support, U.S. Gov't, P.H.S.

Descriptors: *Bladder--pathology--PA; *Cell Degranulation--physiology--PH; *Central Nervous System Viral Diseases--complications--CO; *Cystitis --virology--VI; *Mast Cells--physiology--PH; *Neurogenic Inflammation --virology--VI; *Pseudorabies--complications--CO; Administration, Intravesical; Analysis of Variance; Animals; **Bladder** --drug effects--DE; Bladder --innervation--IR; Capsaicin--pharmacology--PD; Cell Degranulation--drug effects--DE; Cystitis--pathology--PA; Cystitis--urine--UR; Denervation; Disease Models, Animal; Diterpenes--administration and dosage--AD; Diterpenes--pharmacology--PD; Histamine--urine--UR; Mast Cells --drug

effects--DE; Neurogenic Inflammation--pathology--PA; Neurogenic Inflammation--urine--UR; Neurons, Afferent--drug effects--DE; **Neurotoxins** --administration and dosage--AD; **Neurotoxins** --pharmacology--PD; Rats; Rats, Sprague-Dawley

CAS Registry No.: 0 (Diterpenes); 0 (Neurotoxins); 404-86-4 (Capsaicin); 51-45-6 (Histamine); 57444-62-9 (resiniferatoxin)

Record Date Created: 20000914

Record Date Completed: 20000914

10/9/5 (Item 5 from file: 156)

DIALOG(R)File 156:ToxFile

3426006 NLM Doc No: 10953167

CNS induced neurogenic cystitis is associated with bladder mast cell degranulation in the rat.

Jasmin L; Janni G; Ohara P T; Rabkin S D

Departments of Neurosurgery, Cell Biology, Microbiology & Immunology, Georgetown University Medical Center, Washington, DC, USA.

Journal Name: Journal of urology (UNITED STATES) Pub. Year: Sep 2000 164 (3 Pt 1) p852-5, ISSN: 0022-5347 Journal Code: 0376374

Contract/Grant No.: AR46085; AR; NIAMS

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: Toxbib ; AIM; INDEX MEDICUS

PURPOSE: To determine if bladder mast cell degranulation is involved in the genesis of neurogenic cystitis induced by pseudorabies virus (PRV) invasion of the central nervous system (CNS). MATERIALS AND METHODS: Rats received a total of 4 x 106 plaque forming units (pfu) of PRV-Bartha in the abductor caudalis dorsalis (ACD) muscle. Granulated bladder mast cells per mm2 of bladder tissue and urine histamine content were monitored as the cystitis developed over the next few days. In a subgroup of rats, intravesical resiniferatoxin was used to remove capsaicin-sensitive sensory bladder afferents, while another subgroup was pretreated with a mast cell degranulator. RESULTS: PRV injection into the ACD muscle leads to neurogenic cystitis. Histamine levels were elevated in the urine of virus injected rats before any behavioral or microscopical signs of cystitis were present. When the cystitis became clinically manifest, urine histamine returned to control levels, and the number of granulated mast cells dropped significantly. Rats in which capsaicin-sensitive afferents had been removed did not show any signs of cystitis, or increase in urine histamine, or change in the number of granulated mast cells. Pretreatment of animals with a mast cell degranulator completely prevented the appearance of cystitis without altering the CNS disease. CONCLUSION: These results provide further evidence that mast cells are involved in neurogenic cystitis induced by changes in CNS activity.

Tags: Male; Research Support, U.S. Gov't, P.H.S.

Descriptors: *Bladder--pathology--PA; *Cell Degranulation--physiology--PH ; *Central Nervous System Viral Diseases--complications--CO; *Cystitis --virology--VI; *Mast Cells--physiology--PH; *Neurogenic Inflammation --virology--VI; *Pseudorabies--complications--CO; Administration, Intravesical; Analysis of Variance; Animals; **Bladder** --drug effects--DE; Bladder --innervation--IR; Capsaicin--pharmacology--PD; Cell Degranulation--drug effects--DE; Cystitis--pathology--PA; Cystitis--urine--UR; Denervation; Disease Models, Animal; Diterpenes--administration and dosage--AD; Diterpenes--pharmacology--PD; Histamine--urine--UR; Mast Cells --drug

effects--DE; Neurogenic Inflammation--pathology--PA; Neurogenic Inflammation--urine--UR; Neurons, Afferent--drug effects--DE; **Neurotoxins** --administration and dosage--AD; **Neurotoxins** --pharmacology--PD; Rats; Rats, Sprague-Dawley
CAS Registry No.: 0 (Diterpenes); 0 (Neurotoxins); 404-86-4 (Capsaicin); 51-45-6 (Histamine); 57444-62-9 (resiniferatoxin)
Record Date Created: 20000914
Record Date Completed: 20000914

10/9/6 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08912990 Genuine Article#: 343BP Number of References: 40
Title: Botulinum-a toxin for treating detrusor hyperreflexia in spinal cord injured patients: A new alternative to anticholinergic drugs? Preliminary results
Author(s): Schurch B (REPRINT) ; Stohrer M; Kramer G; Schmid DM; Gaul G; Hauri D
Corporate Source: UNIV HOSP BALGRIST,SWISS PARAPLEG CTR/CH-8008 ZURICH//SWITZERLAND/ (REPRINT); UNIV ZURICH HOSP,DEPT UROL/ZURICH//SWITZERLAND/; BG UNFALLKLIN,/MURNAU//SWITZERLAND/
Journal: JOURNAL OF UROLOGY, 2000, V164, N3,1 (SEP), P692-697
ISSN: 0022-5347 Publication date: 20000900
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621
Language: English Document Type: ARTICLE
Geographic Location: SWITZERLAND
Subfile: CC LIFE--Current Contents, Life Sciences; CC CLIN--Current Contents, Clinical Medicine;
Journal Subject Category: UROLOGY & NEPHROLOGY
Abstract: Purpose: We evaluated the efficacy of botulinum-A toxin injections into the detrusor muscle in patients with spinal cord injury, detrusor hyperreflexia and urge incontinence resistant to anticholinergic drugs. The purpose of treatment was to suppress incontinence episodes and increase functional bladder capacity.

Materials and Methods: Included in our prospective nonrandomized study done at 2 clinics were 31 patients with traumatic s[illegible]cord injury who emptied the bladder by intermittent self-cathe These patients had severe detrusor hyperreflexia and inc despite a high dose of anticholinergic medication. Pretr evaluation included a clinical examination and complete investigation. Under cystoscopic control a total of 200 botulinum-A toxin were injected into the detrusor muscl sites (10 units per mi. per site), sparing the trigone. urodynamic followup was planned for 6, 16 and 36 weeks Patients were asked to decrease their intake of antich during week 1 after treatment.

Results: Of the 21 patients 19 underwent a comple weeks after the botulinum-A toxin injections, and 11 at [illegible] weeks. At the 6-week followup complete continence was restored in [illegible] 19 cases in which anticholinergic medication was markedly decreased or withdrawn. Less satisfactory results in 2 cases were associated with an insufficient dose of 200 units botulinum-A toxin. After the injections overall mean reflex volume and mean maximum cystometric bladder capacity plus or minus standard deviation significantly increased from 215.8 +/- 90.4 mi. to 415.7 +/- 211.1 (p <0.016) and 296.3 +/- 145.2 to 480.5 +/- 134.1 (p <0.016), respectively. There was also a significant

decrease after treatment in mean maximum detrusor voiding pressure from 65.6 +/- 29.2 cm. water to 35 +/- 32.1 (p <0.016). Mean post-void residual urine volume catheterized at the end of the urodynamic examination increased significantly fi om a mean of 261.8 +/- 241.3 mi. to 490.5 +/- 204.8 (p <0.016). Moreover, autonomic dysreflexia associated with bladder emptying that manifested as a hypertensive crisis during voiding disappeared after treatment in the 3 patients with tetraplegia. Satisfaction was high in all successfully treated patients and no side effects were observed. Ongoing improvement in urodynamic parameters and incontinence was already present in all patients reevaluated at 16 and 36 weeks.

Conclusions: Botulinum-A. toxin injections into the detrusor seem to be a safe and valuable therapeutic option in spinal cord injured patients with incontinence resistant to anticholinergic medication who perform clean intermittent self-catheterization. Successfully treated patients become continent again and may withdraw from or markedly decrease anticholinergic drug intake. A dose of 300 units botulinum-A toxin seems to be needed to counteract an overactive detrusor. The duration of bladder paresis induced by the toxin is at least 9 months, when repeat injections are required.

Descriptors--Author Keywords: bladder ; bladder ; neurogenic ; spinal cord injuries ; botulinum toxin type A ; urinary incontinence

Identifiers--KeyWord Plus(R): INTRAVESICAL CAPSAICIN; OVERACTIVE **BLADDER** ; RESINIFERATOXIN; INJECTION; BLEPHAROSPASM; INCONTINENCE; **NEUROTOXINS**; ACHALASIA; HUMANS

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US006790207B2

(12) **United States Patent**
Utley et al.

(10) **Patent No.: US 6,790,207 B2**
(45) **Date of Patent: Sep. 14, 2004**

(54) **SYSTEMS AND METHODS FOR APPLYING A SELECTED TREATMENT AGENT INTO CONTACT WITH TISSUE TO TREAT DISORDERS OF THE GASTROINTESTINAL TRACT**

(75) Inventors: **David S. Utley**, San Carlos, CA (US); **John W Gaiser**, Mountain View, CA (US); **Rachel Croft**, San Francisco, CA (US)

(73) Assignee: **Curon Medical, Inc.**, Fremont, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 09/994,375

(22) Filed: Nov. 26, 2001

(65) **Prior Publication Data**

US 2002/0082670 A1 Jun. 27, 2002

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/304,737, filed on May 4, 1999, now Pat. No. 6,464,697, and a continuation-in-part of application No. 09/090,794, filed on Jun. 4, 1998, now abandoned.

(51) **Int. Cl.**[7] **A61B 18/18**
(52) **U.S. Cl.** **606/41**; 128/898; 607/133
(58) **Field of Search** 606/41, 42; 607/101-105, 607/115, 116, 133; 128/898

(56) **References Cited**

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3,901,241	A	8/1975	Allen, Jr.
4,011,872	A	3/1977	Komiya
4,196,724	A	4/1980	Wirt et al.
4,313,958	A	2/1982	LaHann
4,411,266	A	10/1983	Cosman
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EP	0 139 607	5/1985

(List continued on next page.)

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Castell, D.O. "Gastroesophageal Reflux Disease: Current Strategies for Patient Management." Arch Fam Med. 5(4):221-7.

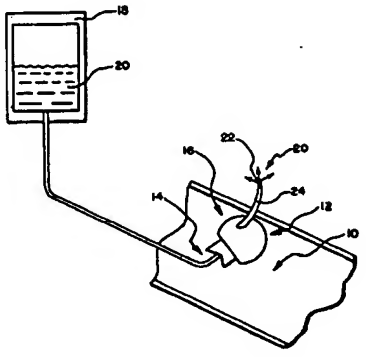
(List continued on next page.)

Primary Examiner—Michael Peffley
(74) *Attorney, Agent, or Firm*—Ryan Kromholz & Manion, S.C.

(57) **ABSTRACT**

Systems and methods that treat disorders of the gastrointestinal tract by applying one or more treatment agents to tissue at or near the region where abnormal neurological symptoms or abnormal tissue conditions exist. The treatment agent is selected to either disrupt the abnormal nerve pathways and/or to alleviate the abnormal tissue conditions. The treatment agent can include at least one cytokine and/or at least one vanilloid compound to evoke a desired tissue response. The systems and methods can be used a primary treatment modality, or as a neoadjuvent or adjuvant treatment modality.

4 Claims, 3 Drawing Sheets



L2: Entry 6 of 18 File: USPT Sep 14, 2004

DOCUMENT-IDENTIFIER: US 6790207 B2
TITLE: Systems and methods for applying a selected treatment agent into contact with tissue to treat disorders of the gastrointestinal tract

Detailed Description Text (23):
Synthetic vanilloid compounds such as synthetic capsaicin are disclosed in WO 96/40079, which is incorporated herein by reference. The vanilloid compound family includes: Capsaicin; Dihydrocapsaicin: Nordihydrocapsaicin; Homocapsaicin: Homodihydrocapsaicin. Alternatively, resiniferotoxin (RTX) is derived from the euphorbia cactus and is considered a capsaicin-like compound. This substance also activates the VR1 receptor and attenuates or eliminates afferent nerve function, although it may not illicit the rapid heat sensation that other vanilloids produce.

Detailed Description Text (24):
Other examples of vanilloid compounds include capsaicin ((E)-(N)-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-6-nonenamide); eugenol (2-methoxy-4-(2-propenyl) phenol); zingerone (4-(4-hydroxy-3-methoxyphenyl)-2-butanone); curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione); piperine (1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl] piperidine); resiniferatoxin(6,7-deepoxy-6,7-didehydro-5-deoxy-21-dephenyl-21-(phenylme thyl)-20-(4-hydroxy-3-thoxybenzeneacetate)) or pharmaceutically effective salts, analogues, derivatives or equivalents thereof.

Detailed Description Text (30):
An example of vanilloid materials that can be used is produced by Afferon and is called RTX, which has been instilled into the lumen of the urinary bladder for the treatment of urge incontinence. There are also several topical, over-the-counter capsaicin products for topical analgesic applications.

L2: Entry 6 of 18 File: USPT Sep 14, 2004

US-PAT-NO: 6790207
DOCUMENT-IDENTIFIER: US 6790207 B2

TITLE: Systems and methods for applying a selected treatment agent into contact with tissue to treat disorders of the gastrointestinal tract

DATE-ISSUED: September 14, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Utley; David S.	San Carlos	CA		
Gaiser; John W	Mountain View	CA		
Croft; Rachel	San Francisco	CA		

US-CL-CURRENT: 606/41; 128/898, 607/133

CLAIMS:

We claim:

1. A method for treating a tissue region within a body where dysmotility and/or abnormal nerve impulses causing visceral pain exist comprising the steps of identifying the tissue region where dysmotility and/or abnormal nerve impulses causing visceral pain exist, selecting at least one vanilloid compound, providing a source of the at least one vanilloid compound, deploying a catheter carrying on its distal end a tissue-piercing element adjacent to the tissue region, coupling the catheter to the source of the at least one vanilloid compound, and applying through the tissue-piercing element a treatment agent including the at least one vanilloid compound into contact with the tissue region to disrupt the abnormal nerve impulses.

2. A method for treating a tissue region within a body where excess tissue volume exists comprising the steps of identifying the tissue region where excess tissue volume exists, selecting at least one cytokine subtype compound, providing a source of the at least one cytokine subtype compound, deploying a catheter carrying on its distal end a tissue-piercing element adjacent to the tissue region, coupling the catheter to the source of the at least one cytokine subtype compound, delivering radiofrequency energy through the catheter to induce a wound healing response, and applying through the tissue-piercing element a treatment agent including the at least one cytokine subtype into contact with the tissue region to facilitate more exuberant wound healing resulting in a reduction of tissue volume.

3. A method according to claim 1 further including the step of applying radiofrequency energy to incite a wound in the tissue region to which the treatment agent is applied.

4. A method according to claim 1 or 2 wherein the treatment agent is injected

into subsurface tissue.

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US006802841B2

(12) **United States Patent**
Utley et al.

(10) **Patent No.: US 6,802,841 B2**
(45) **Date of Patent: Oct. 12, 2004**

(54) **SYSTEMS AND METHODS FOR APPLYING A SELECTED TREATMENT AGENT INTO CONTACT WITH TISSUE TO TREAT SPHINCTER DYSFUNCTION**

(75) Inventors: **David S Utley**, San Carlos, CA (US); **John W Galser**, Mountain View, CA (US); **Rachel Croft**, San Francisco, CA (US)

(73) Assignee: **Curon Medical, Inc.**, Fremont, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 09/994,379

(22) Filed: Nov. 26, 2001

(65) **Prior Publication Data**

US 2002/0115992 A1 Aug. 22, 2002

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/304,737, filed on May 4, 1999, now Pat. No. 6,464,697, and a continuation-in-part of application No. 09/556,169, filed on Apr. 21, 2000, now Pat. No. 6,645,201, and a continuation-in-part of application No. 09/090,794, filed on Jun. 4, 1998, now abandoned.

(60) Provisional application No. 60/143,749, filed on Jul. 14, 1999.

(51) **Int. Cl.**[7] **A61B 18/18**

(52) **U.S. Cl.** **606/41**; 128/898; 607/133

(58) **Field of Search** 606/1, 27, 28, 606/41, 42; 607/101–105, 115, 116, 133; 604/21, 22

(56) **References Cited**

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4,423,812	A	1/1984	Sato
4,532,924	A	8/1985	Auth et al.

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EP	0 139 6047	5/1985
EP	0 608 609	8/1994
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Hinder, R.A., et al.; "The Technique of Laparoscopic Nissen Fundoplication: Surgical Laparoscopy and Endoscopy." 1992.2(3): 265–272.

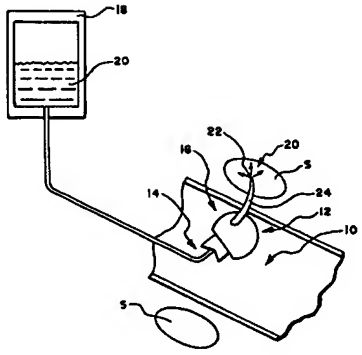
(List continued on next page.)

Primary Examiner—Michael Peffley
(74) *Attorney, Agent, or Firm*—Ryan Kromholz & Manion, S.C.

(57) **ABSTRACT**

Systems and methods apply a selected treatment agent or agents into contact with tissue at or in the region of a dysfunctional sphincter (in the case of GERD, fecal incontinence, or other dysfunctional sphincter disorders) to affect improved sphincter barrier function and/or to disrupt abnormal nerve pathways. The treatment agent can include at least one cytokine and/or at least one tissue bulking agent and/or at least one vanilloid compound to evoke a desired tissue response. The systems and methods can be used a primary treatment modality, or applied as a supplementary treatment before, during or after a primary intervention.

6 Claims, 10 Drawing Sheets



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L2: Entry 5 of 18 File: USPT Oct 12, 2004

US-PAT-NO: 6802841
DOCUMENT-IDENTIFIER: US 6802841 B2
** See image for Certificate of Correction **

TITLE: Systems and methods for applying a selected treatment agent into contact with tissue to treat sphincter dysfunction

DATE-ISSUED: October 12, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Utley; David S	San Carlos	CA		
Gaiser; John W	Mountain View	CA		
Croft; Rachel	San Francisco	CA		

US-CL-CURRENT: 606/41; 128/898, 607/133

CLAIMS:

We claim:

1. A method for treating a tissue region at or near a sphincter comprising the steps of selecting at least one cytokine subtype, providing a source of the at least one cytokine subtype, deploying a catheter carrying on its distal end a tissue-piercing element adjacent a tissue region at or near a sphincter, coupling the catheter to the source of the at least one cytokine subtype, delivering radiofrequency energy through the catheter to induce a wound healing response, and applying through the tissue-piercing element a treatment agent including the at least one cytokine subtype into contact with the tissue region.

2. A method for treating a tissue region at or near a sphincter comprising the steps of selecting at least one vanilloid compound, providing a source of the at least one vanilloid compound, deploying a catheter carrying on its distal end a tissue-piercing element adjacent a tissue region at or near a sphincter, coupling the catheter to the source of the at least one vanilloid compound, and applying through the tissue-piercing element a treatment agent including the at least one vanilloid compound into contact with the tissue region.

3. A method according to claim 1 or 2 wherein the treatment agent is injected into subsurface tissue.

4. A method according to claim 2 further including the step of applying radiofrequency energy to incite a wound in the tissue region to which the treatment agent is applied.

5. A method for treating a tissue region at or near a sphincter comprising the

steps of selecting at least one tissue bulking agent, providing a source of the at least one tissue hulking agent, deploying a catheter carrying on its distal end a tissue-piercing element adjacent a tissue region at or near a sphincter, coupling the catheter to the source of the at least one tissue bulking agent, and applying through the tissue-piercing element a treatment agent including the at least one tissue hulking agent into contact with the tissue region.

6. A method according to claim 5 wherein the treatment agent is injected into subsurface tissue.

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US006802841B2

(12) **United States Patent**
Utley et al.

(10) **Patent No.: US 6,802,841 B2**
(45) **Date of Patent: Oct. 12, 2004**

(54) **SYSTEMS AND METHODS FOR APPLYING A SELECTED TREATMENT AGENT INTO CONTACT WITH TISSUE TO TREAT SPHINCTER DYSFUNCTION**

(75) Inventors: **David S Utley**, San Carlos, CA (US); **John W Gaiser**, Mountain View, CA (US); **Rachel Croft**, San Francisco, CA (US)

(73) Assignee: **Curon Medical, Inc.**, Fremont, CA (US)

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(52) **U.S. Cl.** **606/41**; 128/898; 607/133

(58) **Field of Search** 606/1, 27, 28, 606/41, 42; 607/101–105, 115, 116, 133; 604/21, 22

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Primary Examiner—Michael Peffley
(74) *Attorney, Agent, or Firm*—Ryan Kromholz & Manion, S.C.

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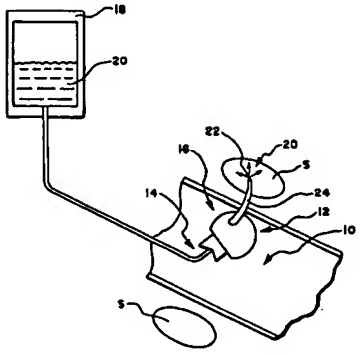
6 Claims, 10 Drawing Sheets



L2: Entry 5 of 18 File: USPT Oct 12, 2004

DOCUMENT-IDENTIFIER: US 6802841 B2
** See image for Certificate of Correction **
TITLE: Systems and methods for applying a selected treatment agent into contact with tissue to treat sphincter dysfunction

Detailed Description Text (38):
Synthetic vanilloid compounds such as synthetic capsaicin are disclosed in WO 96/40079, which is incorporated herein by reference. The vanilloid compound family includes: Capsaicin; Dihydrocapsaicin: Nordihydrocapsaicin; Homocapsaicin; Homodihydrocapsaicin. Alternatively, resiniferotoxin (RTX) is derived from the euphorbia cactus and is considered a capsaicin-like compound. This substance also activates the VR1 receptor and attenuates or eliminates afferent nerve function, although it may not illicit the rapid heat sensation that other vanilloids produce.

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Other examples of vanilloid compounds include capsaicin ((E)-(N)-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-me thyl-6-nonenamide); eugenol (2-methoxy-4-(2-propenyl) phenol); zingerone (4-(4-hydroxy-3-methoxyphenyl)-2-butanone); curcumin (1,7-bis(4-hydroxy-3-methoxy-phenyl)1,6-heptadiene-3,5-dione); piperine (1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl] piperidine); resiniferatoxin(6,7-deepoxy-6,7-didehydro-5-deoxy-21-de-phenyl-21-(phenylm ethyl)-20-(4-hydroxy-3-thoxybenzene-acetate)) or pharmaceutically effective salts, analogues, derivatives or equivalents thereof. The treatment agent 20 can include capsaicin, another vanilloid compound, RTX, or combination thereof, alone or in combination with other substances (which will be generically called a vanilloid-containing treatment agent 20).

Detailed Description Text (45):
An example of vanilloid materials that can be used is produced by Afferon and is called RTX, which has been instilled into the lumen of the urinary bladder for the treatment of urge incontinence. There are also several topical, over-the-counter capsaicin products for topical analgesic applications.

US005698549A

United States Patent [19]

Steers et al.

[11] Patent Number: 5,698,549

[45] Date of Patent: Dec. 16, 1997

[54] **METHOD OF TREATING HYPERACTIVE VOIDING WITH CALCIUM CHANNEL BLOCKERS**

[75] Inventors: **William D. Steers**, Charlottesville; **Jeremy B. Tuttle**, Earlysville, both of Va.

[73] Assignee: **UVA Patent Foundation**, Charlottesville, Va.

[21] Appl. No.: **474,979**

[22] Filed: **Jun. 7, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 241,776, May 12, 1994, Pat. No. 5,503,986.

[51] **Int. Cl.**[6] **A61K 31/55; A61K 31/135**

[52] **U.S. Cl.** **514/211**; 514/654

[58] **Field of Search** 514/211, 654

[56] **References Cited**

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Primary Examiner—William R.A. Jarvis

Attorney, Agent, or Firm—Sheldon H. Parker

[57] **ABSTRACT**

The instant invention discloses a method of treating hyperactive voiding associated with excessive nerve growth factor production and nerve growth in patients by administering a Ca^{++} channel blocker. The Ca^{++} channel blockers verapamil and diltiazem can be administered systemically to treat hyperactive voiding, such as is associated with benign prostatic hyperplasia and interstitial cystitis.

6 Claims, 13 Drawing Sheets

L2: Entry 13 of 18 File: USPT Dec 16, 1997

DOCUMENT-IDENTIFIER: US 5698549 A
TITLE: Method of treating hyperactive voiding with calcium channel blockers

Detailed Description Text (22):
Significant increase in nerve fibers in the sub-urothelial and detrusor muscle layers in patients with IC, but not those with lupus-associated cystitis, indicates neurotrophic involvement. Cell types associated with IC inflammation, including mast cells, release substances that promote neural growth. Cystolysis, however reversed the sub-urothelial nerve proliferation. Many treatments for IC are based upon bladder de-afferentation, high-lighting the importance of this pathway in symptoms. Intravesical infusions of the sensory neurotoxin capsaicin have also been reported to reverse irritative voiding in IC, suggesting removal of the capsaicin-sensitive afferents ameliorates the symptoms. However, these treatments may ultimately be self-defeating. In the rat, denervation of the hemi-bladder increases bladder NGF and causes the remaining neurons to grow. An increased nerve fiber density is precisely what results from an increased supply of potent neurotrophic factors. Because neurotrophic factors regulate neural growth and afferent signaling in the adult, a role for factor-mediated neural changes is likely, before and after treatment. Therefore, it appears that bladder afferents grow and alter their responsive signaling after acute and chronic inflammatory stimuli in animals, and that IC in humans is also accompanied by nerve growth. Reinnervation can explain why the IC symptoms return or worsen after many treatments that could potentially cause denervation.

Detailed Description Text (36):
Under halothane anesthesia bladders are removed intact with a segment of urethra still attached. To standardize the conditions of muscle distention independent of the degree of enlargement, the bladders were fixed. After weighing the bladder, the urethra was cannulated with a 20 gauge needle and a ligature was placed around the needle at the bladder neck. The bladder lumen was filled with a fixative (1 ml of 10% formalin per 100 mg bladder weight) and the bladder was immersed in the fixative for 4 minutes. These bladders were then fixed overnight in 4% buffered formalin and stained with hematoxylin and eosin. Transverse sections cut at 14 .mu.m were inspected with light microscopy for evidence of muscle hypertrophy.

US 20030161809A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2003/0161809 A1

Houston et al. (43) Pub. Date: Aug. 28, 2003

(54) COMPOSITIONS AND METHODS FOR THE TRANSPORT OF BIOLOGICALLY ACTIVE AGENTS ACROSS CELLULAR BARRIERS

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(21) Appl. No.: 09/969,748

(22) Filed: Oct. 2, 2001

Related U.S. Application Data

(60) Provisional application No. 60/237,929, filed on Oct. 2, 2000. Provisional application No. 60/248,478, filed on Nov. 13, 2000. Provisional application No. 60/248,819, filed on Nov. 14, 2000. Provisional application No. 60/267,601, filed on Feb. 9, 2001.

Publication Classification

(51) Int. Cl.[7] A61K 39/395; C12Q 1/68; A61K 38/20; A61K 48/00; C07K 14/52; C07K 16/46

(52) U.S. Cl. 424/85.2; 424/178.1; 514/44; 435/6; 530/351; 530/391.1; 530/395

(57) ABSTRACT

Disclosed herein are complexes and compounds that pass through cellular barriers to deliver compounds into, through and out of cells, and methods of producing and using such complexes and compounds. The complexes and compounds of the invention comprise a biologically active portion and a targeting element directed to a ligand that confers transcellular, transcytotic or paracellular transporting properties to an agent specifically bound to the ligand, with the proviso that the targeting element is not an antibody. Also disclosed are complexes and compounds that comprise two or more targeting elements directed to a ligand that confers transcellular, transcytotic or paracellular transporting properties to an agent specifically bound to the ligand. Preferred ligands include but are not limited to the stalk of pIgR, a pIgR domain, an amino acid sequence that is conserved among pIgR's from different animals, and one of several regions of pIgR defined herein.

DOCUMENT-IDENTIFIER: US 20040260272 A1
TITLE: Method and system for intravesicular delivery of therapeutic agents

Detail Description Paragraph:
[0069] The innermost layer of the bladder wall 12, urothelium 32, functions physiologically in the accommodation and storage of urine, maintenance of urine composition, facilitation of voiding and containment of potential toxins within the bladder to prevent their systemic absorption. The urothelium has three cellular zones: a basal layer, which is the outermost layer with respect to the interior of the bladder and contains cells which are mostly germinal in nature; an intermediate cell layer; and an innermost layer which lines the lumen of bladder 10 and comprises epithelial umbrella cells. The luminal surfaces of the umbrella cells are coated with a layer of glycosaminoglycans. This anatomy is illustrated in more detail in FIG. 16 and may be better understood from the description of that figure set forth below.

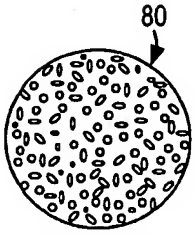

FIG. 7

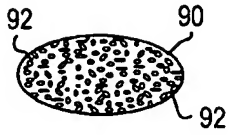

FIG. 8

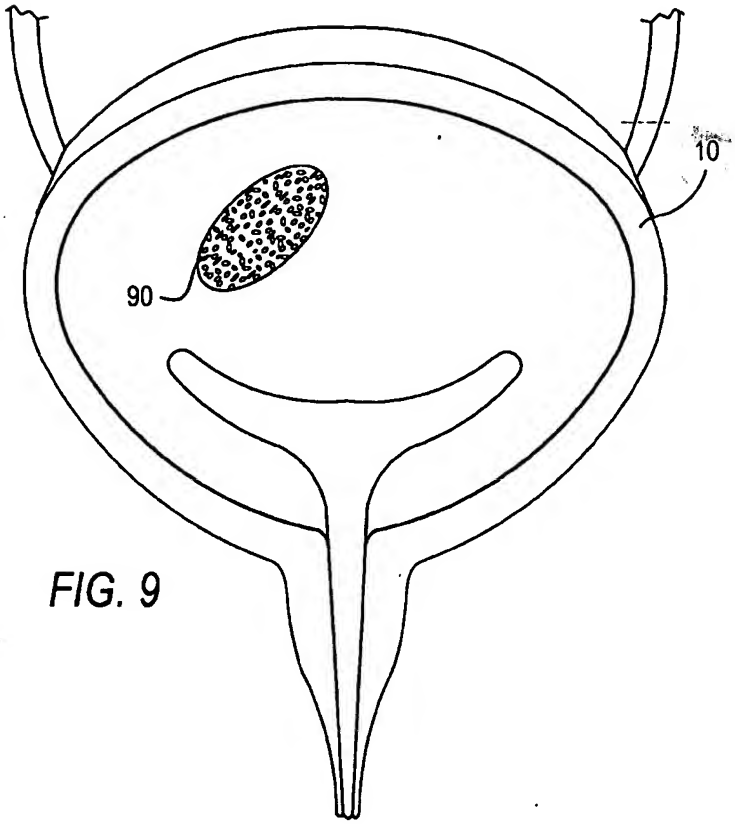

FIG. 9

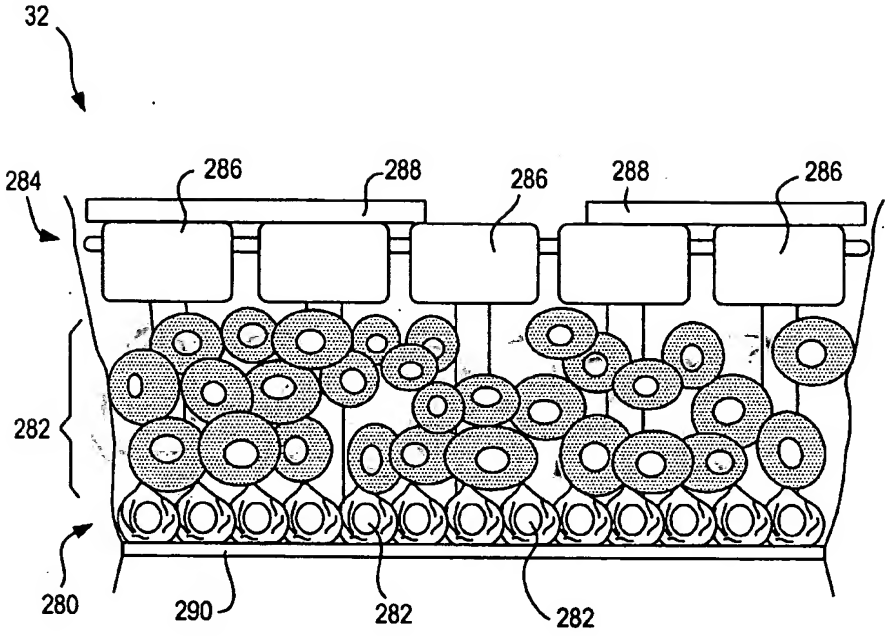

FIG. 21

US005354278A

United States Patent [19]

Kriesel

[11] Patent Number: 5,354,278

[45] Date of Patent: * Oct. 11, 1994

[54] FLUID DISPENSER

[75] Inventor: Marshall S. Kriesel, Bloomington, Minn.

[73] Assignee: Science Incorporated, Bloomington, Minn.

[*] Notice: The portion of the term of this patent subsequent to Nov. 23, 2010 has been disclaimed.

[21] Appl. No.: 53,723

[22] Filed: Apr. 26, 1993

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 870,521, Apr. 17, 1992, Pat. No. 5,263,940.

[51] Int. Cl.[5] A61M 37/00

[52] U.S. Cl. 604/132

[58] Field of Search 604/132, 131, 93, 82, 604/83, 84, 85, 92; 128/DIG. 12

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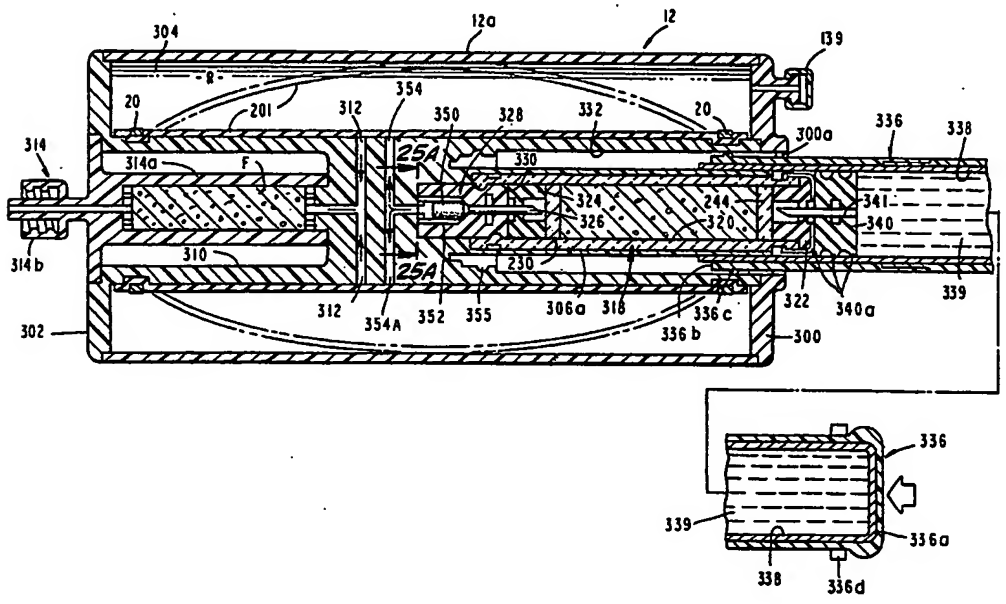
Primary Examiner—Gene Mancene
Assistant Examiner—Jeffrey A. Smith
Attorney, Agent, or Firm—J. E. Brunton

[57] ABSTRACT

An elastomeric bladder type infusion device for delivering a beneficial agent, such as a drug to a patient at substantially a constant rate. The device uniquely includes an internally disposed functional substrate which carries the beneficial agent so that it can be mixed with the fluid as the fluid is being introduced into the device to distend the bladder to make it an energy source for controllably dispensing the solution mixture to a patient.

39 Claims, 15 Drawing Sheets



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DOCUMENT-IDENTIFIER: US 5354278 A
TITLE: Fluid dispenser

Brief Summary Text (5):
Another type of balloon type infusion device is disclosed in U.S. Pat. No. 4,386,929 issued to Perry, et al. The Perry, et al. device has spaced apart inlet and outlet means and the bladder which is capable of expanding and contracting radially and axially upon inflation and deflation. When deflated the lumen of the bladder is substantially completely filled by lumen filling means which protect the bladder from being punctured by the hypodermic needle used to fill and inflate the bladder. The lumen filling means resists the compressive load applied during insertion of the needle and maintains the inlet and outlet means in spaced apart relationship while providing substantially no resistance to the axial expansion of the bladder. By having the lumen of the bladder filled with the lumen filling means when the bladder is deflated, before its subsequent inflation and deflation, substantially complete expulsion of the fluid contents of the bladder can be obtained.

Detailed Description Text (17):
Biologically Active Material--a substance which is biochemically, immunochemically, physiologically, or pharmaceutically active or reactive. Biologically active material includes at least one or more of the following: biochemical compounds (such as amino acids, carbohydrates, lipids, nucleic acids, proteins, and other biochemicals and substances which may complex or interact with biochemical compounds), such biochemical compounds biologically functioning as antibodies, antigenic substances, enzymes, cofactors, inhibitors, lectins, hormones, hormone producing cells, receptors, coagulation factors, anti-fungal agents, growth enhancers, histones, peptides, vitamins, drugs, cell surface markers and toxins, among others known to those skilled in the art. Of the group of biologically active materials described, proteins are of utmost current interest because of the large molecule genetically engineered bio-pharmaceuticals as those species to be immobilized on the additive carriers hereinafter to be described. A discussion of the use of biomosaic polymers as carriers for biologically active materials is set forth in European Patent Application 0,430,517 A2.

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